Interventions for hirsutism (excluding laser and photoepilation therapy alone) (Review)

van Zuuren EJ, Fedorowicz Z, Carter B, Pandis N

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 4

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Esther J van Zuuren[1], Zbys Fedorowicz[2], Ben Carter[3], Nikolaos Pandis[4]

[1]Department of Dermatology, Leiden University Medical Center, Leiden, Netherlands. [2]Bahrain Branch, Cochrane, Awali, Bahrain. [3]Institute of Primary Care & Public Health, Cardiff University School of Medicine, Cardiff, UK. [4]Department of Orthodontics and Dentofacial Orthopedics, University of Bern, Bern, Switzerland

Contact address: Esther J van Zuuren, Department of Dermatology, Leiden University Medical Center, PO Box 9600, B1-Q, Leiden, 2300 RC, Netherlands. E.J.van_Zuuren@lumc.nl.

Editorial group: Cochrane Skin Group.
Publication status and date: New, published in Issue 4, 2015.
Review content assessed as up-to-date: 11 June 2014.

Citation: van Zuuren EJ, Fedorowicz Z, Carter B, Pandis N. Interventions for hirsutism (excluding laser and photoepilation therapy alone). *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD010334. DOI: 10.1002/14651858.CD010334.pub2.

ABSTRACT

Background

Hirsutism occurs in 5% to 10% of women of reproductive age when there is excessive terminal hair growth in androgen-sensitive areas (male pattern). It is a distressing disorder with a major impact on quality of life. The most common cause is polycystic ovary syndrome. There are many treatment options, but it is not clear which are most effective.

Objectives

To assess the effects of interventions (except laser and light-based therapies alone) for hirsutism.

Search methods

We searched the Cochrane Skin Group Specialised Register, CENTRAL (2014, Issue 6), MEDLINE (from 1946), EMBASE (from 1974), and five trials registers, and checked reference lists of included studies for additional trials. The last search was in June 2014.

Selection criteria

Randomised controlled trials (RCTs) in hirsute women with polycystic ovary syndrome, idiopathic hirsutism, or idiopathic hyperandrogenism.

Data collection and analysis

Two independent authors carried out study selection, data extraction, 'Risk of bias' assessment, and analyses.

Main results

We included 157 studies (sample size 30 to 80) comprising 10,550 women (mean age 25 years). The majority of studies (123/157) were 'high', 30 'unclear', and four 'low' risk of bias. Lack of blinding was the most frequent source of bias. Treatment duration was six to 12 months. Forty-eight studies provided no usable or retrievable data, i.e. lack of separate data for hirsute women, conference proceedings, and losses to follow-up above 40%.

Primary outcomes, 'participant-reported improvement of hirsutism' and 'change in health-related quality of life', were addressed in few studies, and adverse events in only half. In most comparisons there was insufficient evidence to determine if the number of reported

adverse events differed. These included known adverse events: gastrointestinal discomfort, breast tenderness, reduced libido, dry skin (flutamide and finasteride); irregular bleeding (spironolactone); nausea, diarrhoea, bloating (metformin); hot flushes, decreased libido, vaginal dryness, headaches (gonadotropin-releasing hormone (GnRH) analogues)).

Clinician's evaluation of hirsutism and change in androgen levels were addressed in most comparisons, change in body mass index (BMI) and improvement of other clinical signs of hyperandrogenism in one-third of studies.

The quality of evidence was moderate to very low for most outcomes.

There was low quality evidence for the effect of two oral contraceptive pills (OCPs) (ethinyl estradiol + cyproterone acetate versus ethinyl estradiol + desogestrel) on change from baseline of Ferriman-Gallwey scores. The mean difference (MD) was -1.84 (95% confidence interval (CI) -3.86 to 0.18).

There was very low quality evidence that flutamide 250 mg, twice daily, reduced Ferriman-Gallwey scores more effectively than placebo (MD -7.60, 95% CI -10.53 to -4.67 and MD -7.20, 95% CI -10.15 to -4.25). Participants' evaluations in one study with 20 participants confirmed these results (risk ratio (RR) 17.00, 95% CI 1.11 to 259.87).

Spironolactone 100 mg daily was more effective than placebo in reducing Ferriman-Gallwey scores (MD -7.69, 95% CI -10.12 to -5.26) (low quality evidence). It showed similar effectiveness to flutamide in two studies (MD -1.90, 95% CI -5.01 to 1.21 and MD 0.49, 95% CI -1.99 to 2.97) (very low quality evidence), as well as to finasteride in two studies (MD 1.49, 95% CI -0.58 to 3.56 and MD 0.40, 95% CI -1.18 to 1.98) (low quality evidence).

Although there was very low quality evidence of a difference in reduction of Ferriman-Gallwey scores for finasteride 5 mg to 7.5 mg daily versus placebo (MD -5.73, 95% CI -6.87 to -4.58), it was unlikely it was clinically meaningful. These results were reinforced by participants' assessments (RR 2.06, 95% CI 0.99 to 4.29 and RR 11.00, 95% CI 0.69 to 175.86). However, finasteride showed inconsistent results in comparisons with other treatments, and no firm conclusions could be reached.

Metformin demonstrated no benefit over placebo in reduction of Ferriman-Gallwey scores (MD 0.05, 95% CI -1.02 to 1.12), but the quality of evidence was low. Results regarding the effectiveness of GnRH analogues were inconsistent, varying from minimal to important improvements.

We were unable to pool data for OCPs with cyproterone acetate 20 mg to 100 mg due to clinical and methodological heterogeneity between studies. However, addition of cyproterone acetate to OCPs provided greater reductions in Ferriman-Gallwey scores.

Two studies, comparing finasteride 5 mg and spironolactone 100 mg, did not show differences in participant assessments and reduction of Ferriman-Gallwey scores (low quality evidence). Ferriman-Gallwey scores from three studies comparing flutamide versus metformin could not be pooled (I^2 = 62%). One study comparing flutamide 250 mg twice daily with metformin 850 mg twice daily for 12 months, which reached a higher cumulative dosage than two other studies evaluating this comparison, showed flutamide to be more effective (MD -6.30, 95% CI -9.83 to -2.77) (very low quality evidence). Data showing reductions in Ferriman-Gallwey scores could not be pooled for four studies comparing finasteride with flutamide as the results were inconsistent (I^2 = 67%).

Studies examining effects of hypocaloric diets reported reductions in BMI, but which did not result in reductions in Ferriman-Gallwey scores. Although certain cosmetic measures are commonly used, we did not identify any relevant RCTs.

Authors' conclusions

Treatments may need to incorporate pharmacological therapies, cosmetic procedures, and psychological support. For mild hirsutism there is evidence of limited quality that OCPs are effective. Flutamide 250 mg twice daily and spironolactone 100 mg daily appeared to be effective and safe, albeit the evidence was low to very low quality. Finasteride 5 mg daily showed inconsistent results in different comparisons, therefore no firm conclusions can be made. As the side effects of antiandrogens and finasteride are well known, these should be accounted for in any clinical decision-making. There was low quality evidence that metformin was ineffective for hirsutism and although GnRH analogues showed inconsistent results in reducing hirsutism they do have significant side effects.

Further research should consist of well-designed, rigorously reported, head-to-head trials examining OCPs combined with antiandrogens or 5α-reductase inhibitor against OCP monotherapy, as well as the different antiandrogens and 5α-reductase inhibitors against each other. Outcomes should be based on standardised scales of participants' assessment of treatment efficacy, with a greater emphasis on change in quality of life as a result of treatment.

PLAIN LANGUAGE SUMMARY

Treatments for unwanted male pattern hair growth in women

Background

Up to 5% to 10% of women are hirsute (hair in areas where normally only men have hairs such as moustache, beard area, chest, belly, back etc). The most common cause is polycystic ovary syndrome. Hirsutism can lead to psychological distress, low self esteem, decreased self image, depression, feelings of shame and social difficulties.

Review question

Which treatments (except laser and light-based therapies alone) work best for hirsutism?

Study characteristics

We included 157 studies published up to June 2014, which examined 10,550 people. Participants included women with a mean age of 25 years. There was considerable variation in the quality of how the studies were conducted; more than half were not blinded and this may have had an impact on the reporting of the outcomes. Most studies were carried out in single centres in Europe and lasted six to 12 months. A range of treatments were evaluated, mostly in single studies. These included a few topical treatments, lifestyle modification, oral contraceptive pills (OCPs), medication to inhibit the effect of hormones that are responsible for male traits, and combination therapies. Participant-assessed improvement and impact on quality of life were evaluated in a minority of the studies, whilst the majority of the studies measured physician-assessed reduction in hirsutism, as well as androgen levels in the blood. Half of the studies reported adverse events and around one-third other signs and symptoms, e.g. oily skin and menstrual irregularities that might be due to an increase of androgen levels in the blood.

Key results

Oral contraceptive pills reduced the amount of hairs, but the reduction was not consistent across the studies, although two OCPs (ethinyl estradiol 35 μg + cyproterone acetate 2 mg compared to ethinyl estradiol 30 μg + desogestrel 0.15 mg) appeared to be effective in a way that can be considered important for women with hirsutism.

Of the antiandrogen drugs, flutamide was considered to be more effective than placebo by both the women and the doctors. Spironolactone was also effective, but data were only available for the physicians' assessments. Finasteride did not show convincing effectiveness based on the evaluations of the hirsute women and those made by the investigators. The addition of cyproterone acetate (an antiandrogen) to OCP seemed to enhance the beneficial effect of OCPs on hair reduction.

Insulin sensitisers (antidiabetic drugs) and lifestyle modification did not have any demonstrable benefit in terms of the severity of hirsutism. Unfortunately, the self assessments by the women, as well as the impact of hirsutism on their quality of life, were outcomes that were insufficiently addressed in the studies.

The adverse events reported with the different drugs are well known, i.e. pain in the stomach and intestines, breast tenderness, reduced libido and dry skin with flutamide and finasteride; irregular bleeding with spironolactone; nausea, diarrhoea and abdominal bloating with metformin; and hot flushes, decreased libido, vaginal dryness, breast tenderness and headaches with the GnRH analogues.

There were no important differences in blood androgen levels between the different treatment groups, OCPs had a positive effect on acne, and similarly insulin sensitisers improved the menstrual pattern.

We were expecting to find evidence that combined therapies of an OCP with an antiandrogen were more effective than, for example, OCPs alone, but the lack of studies did not allow us to draw these conclusions.

Overall we concluded that OCPs (especially with antiandrogenic activity), OCPs combined with cyproterone acetate, flutamide and spironolactone are effective in treating hirsutism. However, additional cosmetic measures (epilating, waxing, bleaching, electrolysis, laser and photoepilation) are generally required because all treatments need at least six to 12 months to reach the optimum effect. In addition, because of the distress associated with hirsutism and its impact on quality of life psychological support should be part of the treatment approach.

Quality of the evidence

The overall quality of the evidence for the different outcomes was on average rated as moderate to very low. Important reasons for this were that studies were not blinded, or had a small sample size.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Ethinyl estradiol 35 μg + cyproterone acetate 2 mg compared to ethinyl estradiol 30 μg + desogestrel 0.15 mg for hirsutism

Patient or population: patients with hirsutism
Intervention: ethinyl estradiol 35 μg + cyproterone acetate 2 mg
Comparison: ethinyl estradiol 30 μg + desogestrel 0.15 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Ethinyl estradiol 30 μg + desogestrel 0.15 mg	Ethinyl estradiol 35 μg + cyproterone acetate 2 mg				
Participant-reported improvement of hirsutism - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants who reported an adverse event	**Study population**		**RR 0.41** (0.08 to 2.05)	100 (1 study)	⊕⊕⊕◯ **moderate**[1]	
	100 per 1000	**41 per 1000** (8 to 205)				
	Low					
	40 per 100	**16 per 1000** (3 to 82)				

Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	The mean clinician's assessment of improvement of hirsutism ranged across control groups from **-1.69 to -9.51**	The mean clinician's assessment of improvement of hirsutism in the intervention groups was **1.84 lower** (3.86 lower to 0.18 higher)		164 (3 studies)	⊕⊕◯◯ **low**[2,3]	Both treatments demonstrated a clinically important reduction in Ferriman-Gallwey score, but the MD between the groups was not statistically significant
Change in serum androgen levels	See comment	See comment	Not estimable	184 (4 studies)	⊕⊕⊕⊕ **high**	There were no clinically important differences in serum androgen levels between the 2 groups
Change in BMI kg/m^2	See comment	See comment	Not estimable	136 (2 studies)	⊕⊕⊕◯ **moderate**[4]	MD -0.14 kg/m^2, 95% CI -2.44 to 2.16; P value = 0.90 (Bhattacharya 2012) and 0.10 kg/m^2, 95% CI -2.85 to 3.05; P value = 0.95 (Mastorakos 2006)
Improvement of other clinical signs of hyperandrogenism Acne score - grade 1 to 4 (higher is worse)	The mean improvement of other clinical signs of hyperandrogenism in the control groups was **-1.41**	The mean improvement of other clinical signs of hyperandrogenism in the intervention groups was **0.11 lower** (0.61 lower to 0.39 higher)		100 (1 study)	⊕⊕⊕◯ **moderate**[5]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious imprecision (95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable harm).

[2]Downgraded one level due to serious risk of performance and detection bias as in 2 of the 3 studies participants, investigators, and outcome assessors were not blinded.

[3]Downgraded one level due to serious imprecision (95% confidence interval around the pooled or best estimate of effect includes both no effect and appreciable benefit).

[4]Downgraded one level due to serious imprecision (wide CI for both studies).

[5]Downgraded one level due to serious imprecision (wide CI).

BACKGROUND

We have listed unfamiliar terms in the glossary of terms in Table 1.

Description of the condition

Definition and prevalence

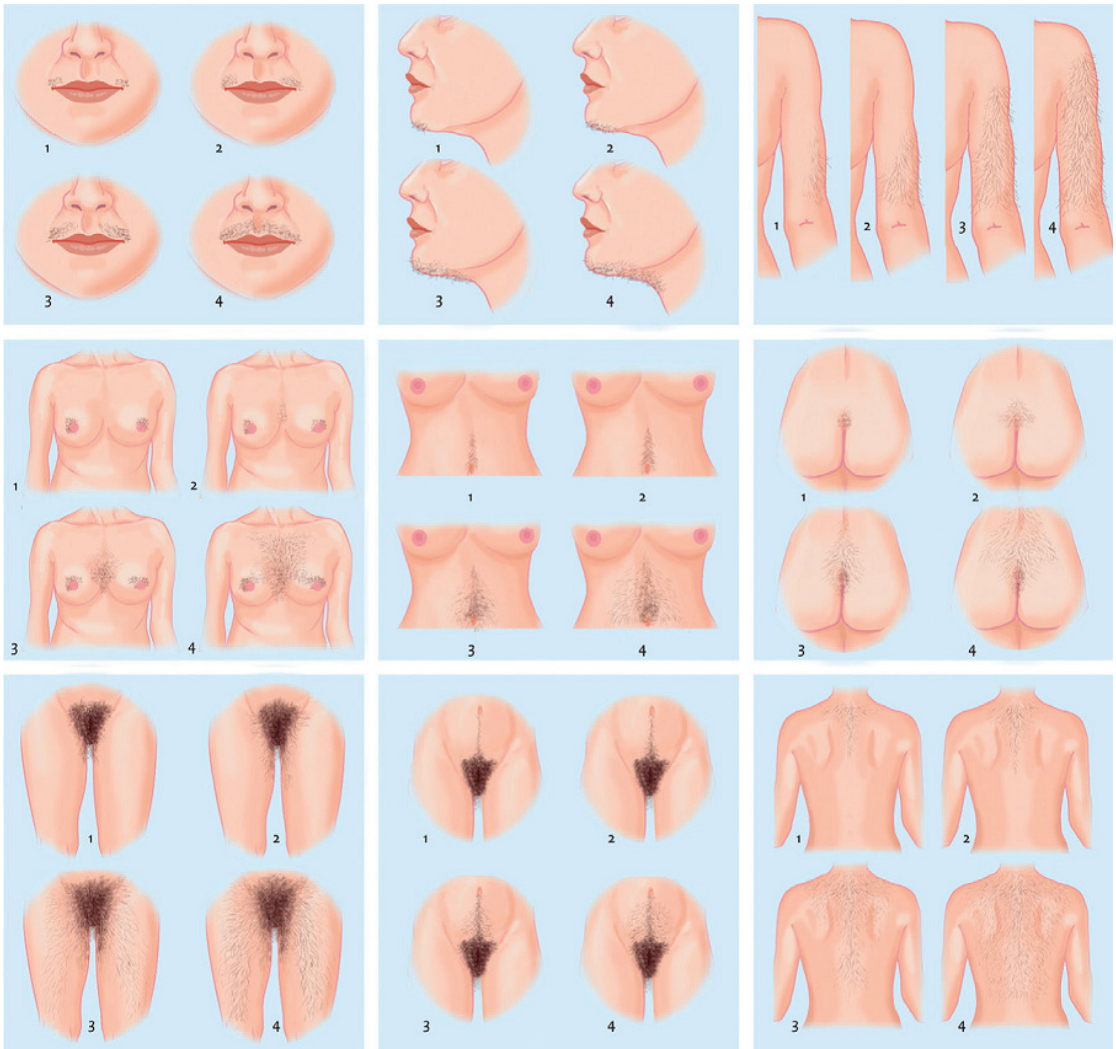
Hirsutism is a condition that occurs when there is an excessive amount of terminal hair growth in androgen-sensitive areas in women (male pattern) (Blume-Peytavi 2009; Brodell 2010) (see Figure 1; Figure 2). It must be differentiated from hypertrichosis, which is androgen-independent (non-sexual pattern) excessive hair growth either generalised or localised on the body (Blume-Peytavi 2011; Bode 2012; Castelo-Branco 2010). Hypertrichosis may be related to ethnic background (Blume-Peytavi 2011), and it can also be caused by metabolic disorders, such as thyroid dysfunction and anorexia nervosa (Bode 2012), or medications, e.g. phenytoin, cyclosporin, and minoxidil (Castelo-Branco 2010; Rosenfield 2005).

Figure 1. Hirsutism on the chin

Figure 2. Hirsutism on the chest and breasts

Approximately 5% to 10% of women of reproductive age are hirsute, as assessed by the Ferriman-Gallwey scoring system (FG) (Cook 2011; Escobar-Morreale 2012; Somani 2008), but in general, a lower percentage of Asian women are affected. This scoring system, which was developed in 1961, scored 11 body sites (upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arm, forearm, thigh, and lower leg) and rated these sites on a four-point scale (0 = 'no hair' to 4 = 'frankly virile') (Cook 2011; Escobar-Morreale 2012; Rosenfield 2005). The subsequently improved modified FG score (mFG method) excludes the forearm and lower leg as these areas are less, or not, sensitive to androgens (Escobar-Morreale 2012; Hatch 1981) (see Figure 3). A score of less than 8 is considered normal, whereas 8 to 15 indicates mild hirsutism, 16 to 25 indicates moderate hirsutism, and a score above 25 indicates severe hirsutism (Escobar-Morreale 2012; Hatch 1981). The limitations of this scoring system are well recognised: it is subjective in nature with wide inter-observer variation; it misses areas such as sideburns and buttocks; and it does not take into account racial and ethnic variability. Additional limitations are the difficulties associated with evaluating the degree of hirsutism in women who are using different treatment methods and also the requirement of a full body examination to score all areas (Bode 2012; Cook 2011; Somani 2008). However, it remains the most widely used scoring method and is considered to be the gold standard in the quantification of hirsutism (Escobar-Morreale 2012). As there is a substantial racial and ethnic variability in terminal hair growth, it has been suggested that lower cut-off values should be used for Asian women, with higher cut-off values for Mediterranean, Middle Eastern, and East Indian women (Escobar-Morreale 2012; Somani 2008).

Figure 3. Modified Ferriman-Gallwey score, each of nine body areas can receive a score from 0 (no hair) to 4 (frankly virile) (van Zuuren EJ, Pijl H. Hirsutism. Ned Tijdschr Geneeskd. 2007 Oct 20;151(42):2313-8



Physiology of hair growth

Five million hair follicles cover the body excluding the palms, soles, mucosae, and glabrous skin of the genitalia and lips (Brodell 2010; Escobar-Morreale 2012). Three types of hair can be distinguished: lanugo hair, which is soft, not pigmented, and sheds sometime late in gestation or early postpartum (Azziz 2003; Lumachi 2010; Shah 2009); vellus hairs, which are short, fine, light-coloured, and barely noticeable but cover most parts of the body; and terminal hairs, which are thicker, longer, and pigmented, and can be found on the scalp and in the axillae, the genital region, eye brows, and eye lashes (Escobar-Morreale 2012; Randall 2008; Shah 2009).

There are three phases of hair growth: anagen, which is the growth phase; catagen, the involuting or regressing phase; and telogen, the resting or quiescent phase (Blume-Peytavi 2011b; Escobar-Morreale 2012; Olsen 1999; Randall 2008).

Androgens stimulate the conversion of vellus into terminal hairs and prolong the anagen phase (Brodell 2010; Paparodis 2011; Randall 2008). Other hormones can also affect hair growth (e.g. growth hormone, thyroid dysfunction), but androgens are considered to play the most significant role. The most important circulating androgen is testosterone, which is secreted in equal amounts from the ovaries (promoted by luteinising hormone (LH) and insulin) and adrenal glands (promoted by adrenocorticotropic

hormone (ACTH) but also through peripheral conversion of androgen precursors (Brodell 2010; Escobar-Morreale 2010; Shah 2009)). Free testosterone is the main bioactive portion of plasma testosterone, but most of the circulating testosterone is bound by sex hormone-binding globulin (SHBG) (Paparodis 2011), which has a high affinity for testosterone and can modulate the bioavailability of free testosterone (Escobar-Morreale 2010; Paparodis 2011). The lower the concentration of serum SHBG, the higher the concentration of free testosterone there will be in the circulation. The more potent dihydrotestosterone is then generated from testosterone by 5-alpha-reductase (5α-reductase) in the hair follicle and stimulates the dermal papilla to produce terminal hairs instead of vellus hairs. Androstenedione and dehydroepiandrosterone (DHEA) are weaker androgens and may also be metabolised in the skin into testosterone and dihydrotestosterone (Azziz 2003). In view of differences in activity of androgen receptors and 5α-reductase content, several regions of the skin are more sensitive to androgens than others (Escobar-Morreale 2012; Randall 2008).

Pathophysiology

Hirsutism is the result of the interaction between circulating androgens and the susceptibility of the hair follicle to androgens (Escobar-Morreale 2012; Rosenfield 2005). Although the majority, but not all, hirsute women exhibit androgen excess (Azziz 2003; Azziz 2004), it is important to differentiate androgen excess (endocrine disease) from hirsutism (dermatological signs) (Azziz 2003). Up to 70% to 80% of women with androgen excess demonstrate hirsutism (Azziz 2004).

The most common cause of hirsutism is polycystic ovary syndrome (PCOS) (Azziz 2003; Blume-Peytavi 2008; Bode 2012), which is one of the most frequently encountered endocrinological disorders in women, with a prevalence of between 5% to 10% (Ekbäck 2009; Guzel 2012); it accounts for 70% to 80% of the cases of hirsutism. According to the revised criteria for diagnosing PCOS, this syndrome is defined if at least two of the following three criteria are present: oligo-ovulation or anovulation; clinical or biochemical signs of hyperandrogenism; or polycystic ovaries, subject to the exclusion of other aetiologies with a similar presentation (Rotterdam Criteria PCOS 2004). Other possible characteristics of women with PCOS besides hirsutism are obesity, acne, insulin resistance, infertility (Azziz 2006; Bode 2012; Brodell 2010), acanthosis nigricans, and female pattern hair loss (Ehrmann 2005; Rosenfield 2005; van Zuuren 2012).

Women affected with idiopathic hyperandrogenism have elevated androgen levels, normal menses, normal ovaries at ultrasound, and no explicable cause for their elevated androgen levels. Idiopathic hyperandrogenism accounts for 6% to 15% of the causes of hirsutism (Bode 2012). Other less common causes of androgen excess are non-classic congenital adrenal hyperplasia and the rarer androgen-secreting tumours (Blume-Peytavi 2008; Bode 2012). Conditions that also lead to androgen excess, but which usually present with other more prominent symptoms are: Cushing's syndrome, acromegaly, thyroid dysfunction, and hyperprolactinaemia (Blume-Peytavi 2008; Bode 2012; Rosenfield 2005). Certain drugs, e.g. anabolic steroids, testosterone, and danazol, can also lead to hirsutism (Blume-Peytavi 2008; Rosenfield 2005).

Idiopathic hirsutism is defined as hirsutism in the presence of regular menses and normal circulating androgen levels (Shah 2009). Increased 5α-reductase activity in the hair follicle or alteration in androgen receptor function may be the underlying cause (Shah 2009; Somani 2008). However, up to 40% of the women diagnosed with idiopathic hirsutism and with a history of regular menstrual cycles appear to be anovulatory and probably suffer from PCOS (Azziz 2003). Idiopathic hirsutism accounts for 4% to 7% of cases (Azziz 2004; Bode 2012), and in line with PCOS, the diagnosis of idiopathic hirsutism is made by gradually excluding other possibilities.

Clinical features and symptoms

Some women with hirsutism have no other clinical features than excessive hair growth, whereas women with hyperandrogenism may exhibit other clinical features, such as acne, seborrhoea, irregular menses or no menses, obesity, and hair loss. Therefore, a full clinical and family history is paramount and should include enquiry about the onset and rate of progression of the hirsutism; a menstrual and reproductive history; presence of acne; hair loss or balding; voice change; weight change; and body contour differences, including the face, enlargement of the clitoris, use of drugs or medication, and prior treatment for hirsutism (Bode 2012; Brodell 2010). Hirsutism is often familial because PCOS has a strong genetic component (Azziz 2003), but idiopathic hirsutism may also frequently be familial (Bode 2012).

Physical examination should involve assessment of the level and extent of hirsutism by the Ferriman-Gallwey score and include measurement of weight, height, body mass index (BMI), examination for acne, seborrhoea, virilisation, abdominal and pelvic masses, features found in Cushing's syndrome (e.g. full moon face and buffalo hump), galactorrhoea, thyroid enlargement, and hair loss (Bode 2012; Escobar-Morreale 2012). Laboratory examination and other investigations, such as ultrasonography, should be done to ensure the correct diagnosis and to exclude other causes of hirsutism (See 'Pathophysiology'). Several reviews have extensively addressed these issues, which are beyond the scope of our Cochrane review (Azziz 2003; Blume-Peytavi 2009; Escobar-Morreale 2012; Koulouri 2009; Rosenfield 2005).

Hirsutism caused by PCOS, idiopathic hyperandrogenism, and idiopathic hirsutism in most cases start around puberty, with slow progression over the years, and are often associated with a family history of hyperandrogenism while signs of virilisation are rare (Escobar-Morreale 2010). A sudden onset and rapid progression of hirsutism accompanied by virilisation is suggestive of androgen-secreting tumours (Escobar-Morreale 2012; Rosenfield 2005).

Hirsutism can lead to psychological distress, low self esteem, decreased self image, depression, feelings of shame, body dysmorphic disorder, and social difficulties, such as social phobia and introversion (Barth 1993; Blume-Peytavi 2009; Ekbäck 2009; Lipton 2006). A hair-free body seems to be the social norm of femininity (Blume-Peytavi 2011; Ekbäck 2009; Tiggeman 1998); thus, women with body hair are considered less sexually attractive, and hirsutism may impinge on a woman's feminine identity (Basow 1998; Housman 2004; Keegan 2003; Tiggeman 1998). Furthermore, hirsutism has been shown to have a negative impact on health-related quality of life (HRQOL) (Loo 2002; Sonino 1993), as is the case with the major cause of hirsutism, PCOS, illustrated by studies using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) (Coffey 2006; Guyatt 2004). Therefore, the work-up for evaluating hirsutism should also include an assessment of psychosomatic or even psychiatric problems, in addition to addressing if the quality of life of that individual has decreased because of hirsutism (Blume-Peytavi 2009). Hirsute women may often consider that physicians are less than sympathetic and consequently experience feelings of rejection; it is important that physicians acknowledge the feelings of the hirsute woman and, notably, the possible impact on her HRQOL (Blume-Peytavi 2011; Ekbäck 2011; Lipton 2006).

Women with hirsutism may consult general practitioners, gynaecologists, endocrinologists, dermatologists, and if required, psychologists or psychiatrists (or both). A multidisciplinary approach to treatment may be necessary and will depend on the setting and the experience of the doctor to whom the hirsute woman has been referred.

Description of the intervention

Treatment should be guided by the degree of severity of hirsutism, the woman's preferences, her reproductive status, the underlying cause, and any potential adverse effects (Bode 2012; Lumachi 2010). The duration of the hair growth cycle varies in different parts of the body, ranging from two to 12 months (scalp hairs have even longer cycles) (Olsen 1999; Paparodis 2011; Randall 2008); therefore, treatment periods of between six and 12 months are often recommended for optimal effect, but continuous treatment may also be necessary (Escobar-Morreale 2012; Rosenfield 2005). Management strategies should focus on reducing the free androgen level, blocking the peripheral androgen (Blume-Peytavi 2008; Escobar-Morreale 2012; Paparodis 2011), and improving cosmetic appearance by the removal of existing hair (Brodell 2010; Castelo-Branco 2010; Escobar-Morreale 2012). These should also aim to reduce the risk of related conditions, such as metabolic disorders, reproductive complaints, and endometrial cancer (Escobar-Morreale 2010; Lumachi 2010), and be directed towards improving quality of life (Blume-Peytavi 2011; Brodell 2010). A combination of treatments is often used to achieve optimum results, and these should preferably include a support strategy to help the individual cope emotionally (Blume-Peytavi 2011).

Currently there are no safe pharmacological treatments available for pregnant or lactating women (Bode 2012).

Available treatment options are listed below:

Lifestyle modification

This might include weight loss and cessation of smoking (Blume-Peytavi 2011; Bode 2012; Castelo-Branco 2010; Escobar-Morreale 2012; Koulouri 2008).

Cosmetic measures

These include:

1. shaving, chemical depilatories, bleaching, plucking, tweezing or threading, and waxing (Bode 2012; Escobar-Morreale 2012; Lanigan 2001);
2. electrolysis in the form of galvanic electrolysis, thermolysis, or a combination of both (Blume-Peytavi 2011; Bode 2012; Escobar-Morreale 2012; Richards 1995); and
3. laser and photo epilation (Escobar-Morreale 2012; Haedersdal 2011; Lanigan 2001; Sadighha 2009).

The review will not include treatment with laser and photoepilation alone because they are covered in another Cochrane review (Haedersdal 2006).

Pharmacological treatments

Topical therapy

Eflornithine hydrochloride 13.9% cream applied twice daily (Blume-Peytavi 2008; Escobar-Morreale 2012; Martin 2008) or finasteride cream (0.25% or 0.5%) (Iraji 2005; Lucas 2001).

Oral contraceptive pills (OCP)

These might include a combination of an oestrogen (often ethinyl estradiol) with a varying progestational agent. The progestins include norethindrone, norgestimate, levonorgestrel, ethynodiol diacetate, norgestrel, desogestrel, norethisterone, or norethynodrel. Progestins with an antiandrogenic effect include drospirenone, chlormadinone, dienogest, and cyproterone acetate (Blume-Peytavi 2011; Escobar-Morreale 2012; Martin 2008; Paparodis 2011; Shah 2009).

Antiandrogens

These include:

1. spironolactone 50 to 200 mg/day (Bode 2012; Escobar-Morreale 2012; Martin 2008);
2. cyproterone acetate (CPA) 50 to 100 mg/day (but in the combined OCP as 2 mg) (Blume-Peytavi 2008; Lumachi 2010; Martin 2008); and

3. non-steroidal antiandrogens, such as flutamide 125 to 250 mg twice daily or bicalutamide 25 mg/day (Blume-Peytavi 2008; Castelo-Branco 2010; Martin 2008).

5α-reductase inhibitor

Finasteride 1 to 5 mg/day (Blume-Peytavi 2008; Brodell 2010; Paparodis 2011).

Insulin-sensitising agents

The following have mainly been used in women with PCOS:

1. metformin 500 to 1000 mg twice daily (Castelo-Branco 2010; Lumachi 2010; Paparodis 2011); and
2. thiazolidinediones, e.g. rosiglitazone 4 mg to 8 mg daily and pioglitazone 10 mg to 30 mg (Blume-Peytavi 2008; Lumachi 2010; Paparodis 2011). The European Medicines Agency withdrew rosiglitazone in 2010 after concerns about an increased risk of cardiovascular events. Pioglitazone has been associated with bladder tumours and has been withdrawn in some countries.

Gonadotropin-releasing hormone analogues

Leuprolide acetate 7.5 mg monthly intramuscularly combined with 25 μg to 50 μg transdermal estradiol (Bode 2012; Lumachi 2010).

Glucocorticoids

Prednisone 5 to 10 mg/day (Bode 2012; Escobar-Morreale 2012; Lumachi 2010).

Miscellaneous treatments options

Other treatments that have been tried for their potential beneficial effect or that appear to have an additional effect on hirsutism are spearmint tea (Grant 2010), statins (Banaszewska 2011; Kaya 2010), ovarian resection (Ashrafinia 2009), acarbose (Ciotta 2001; Penna 2005), inositol (Ciotta 2012; Ciotta 2012B), cimetidine (Lissak 1989) bromocriptine (Murdoch 1987), sibutramine (Sabuncu 2003), clomiphene (Roth 2012), and electro-acupuncture (Jedel 2011).

How the intervention might work

Lifestyle modification

Women who are obese, especially when they have PCOS, should be encouraged to lose weight through a combination of exercise and diet. Weight reduction leads to a lowering of free testosterone, reduction of androgen production by the ovaries, reduction of serum insulin, an increase in SHBG, and improvement in fertility (Blume-Peytavi 2011; Bode 2012; Koulouri 2008). Furthermore, it leads to improvement in the quality of life of the woman by raising self esteem and personal well-being. Cessation of smoking should be encouraged as smoking exacerbates some of the side effects of pharmacological treatments for hirsutism, e.g. cardiovascular events in combination with oral contraceptive drugs (Escobar-Morreale 2012).

Cosmetic measures

1. Shaving, chemical depilatories, bleaching, plucking, tweezing or threading, and waxing are all rapid hair removal methods, but they are only temporarily effective. The most important side effects are irritation or dermatitis. Waxing can also be painful and lead to folliculitis (Blume-Peytavi 2011; Bode 2012; Escobar-Morreale 2012; Lanigan 2001).
2. Electrolysis (galvanic electrolysis, thermolysis, or a combination of both (Blume-Peytavi 2011; Bode 2012; Escobar-Morreale 2012; Richards 1995)), involves the passage of an electric current through a needle inserted into the follicle to destroy the hair bulb. Although results are highly dependent on the skills of the professional providing the treatment, it is effective, but often rather painful, very slow, and expensive and might rarely result in scars. Thermolysis is faster, but it is somewhat less effective and uses a high frequency alternating current, which produces heat in the hair follicle and leads to destruction. The combination or blend method combines both these methods.
3. Laser and photoepilation treatments (Blume-Peytavi 2011; Escobar-Morreale 2012; Haedersdal 2011; Lanigan 2001) are among the fastest growing cosmetic procedures in the US and Europe (Haedersdal 2011), and they are most effective in people with lighter skin and dark-coloured hairs. These treatments are widely discussed in another Cochrane review (Haedersdal 2006).

Pharmacological treatments

Topical therapy

Eflornithine hydrochloride irreversibly inhibits ornithine decarboxylase and suppresses the mitotic activity in the hair follicle, thereby reducing the rate of hair growth (Martin 2008; Paparodis 2011). Common side effects are rash and systemic toxicity after widespread application (Rosenfield 2005). Finasteride is a 5α-reductase inhibitor, more frequently used systemically (see under 5α-reductase inhibitor).

Oral contraceptive pills (OCP)

Oral contraceptive pills inhibit androgen secretion by the ovaries and increase SHBG production by the liver, both leading to less circulating free androgens (Bode 2012; Brodell 2010; Escobar-Morreale 2012). The most important side effect is an increased risk of venous thromboembolism. Other side effects are breast tenderness, headache, and gastrointestinal symptoms.

Antiandrogens

In pregnant women all antiandrogens carry the risk of feminisation of the male foetus and should therefore always be combined with effective contraception in women of childbearing age.

1. Spironolactone is an antagonist of both aldosterone and the androgen receptor (Escobar-Morreale 2012; Lumachi 2010; Martin 2008; Shah 2009). It should not be used in women with renal insufficiency or hyperkalaemia. Irregular menstrual bleeding, headache, hypotension, nausea, and decreased libido are side effects that are mostly dose-dependent.
2. Cyproterone acetate is a 17-hydroxyprogesterone acetate derivative that competes with dihydrotestosterone for the androgen receptor and to a lesser extent inhibits 5α-reductase (Blume-Peytavi 2008; Escobar-Morreale 2012; Lumachi 2010). Well known side effects are liver toxicity, irregular menstrual bleeding, nausea, and decreased libido.
3. Flutamide and bicalutamide are non-steroidal, competitive inhibitors of androgen receptor binding (Blume-Peytavi 2008; Lumachi 2010; Paparodis 2011). The most important side effect, although rare, is hepatotoxicity including fulminant liver failure.

5α-reductase inhibitor

Finasteride is a type II inhibitor of the 5α-reductase enzyme and reduces the conversion of testosterone into dihydrotestosterone (Blume-Peytavi 2008; Paparodis 2011; Shah 2009). Finasteride can, like antiandrogens, lead to feminisation of the male foetus and, very rarely, to liver dysfunction.

Insulin-sensitising agents

Women with PCOS frequently have hyperinsulinaemia. Insulin-sensitising drugs decrease hyperinsulinaemia by increasing insulin sensitivity; the lower insulin levels result in an increase of SHBG, thereby reducing the levels of circulating free androgens (Cosma 2008; Lumachi 2010; Paparodis 2011). Practice guidelines advise against prescribing insulin-sensitising drugs for the sole purpose of hirsutism treatment as the advantages are not proven (Escobar-Morreale 2012; Martin 2008). Possible side effects include gastrointestinal distress, increased risk of cardiovascular events, liver dysfunction, and lactic acidosis.

Gonadotropin-releasing hormone analogues (GnRH)

Gonadotropin-releasing hormone analogue agonists suppress the hypothalamic-pituitary-ovarian axis, inhibiting luteinising hormone and follicle-stimulating hormone, thereby decreasing the secretion of androgens by the ovaries (Bode 2012; Lumachi 2010). When GnRH analogues are not combined with oestrogens, they lead to menopausal symptoms with hot flushes and osteoporosis. As they do not seem to have advantages over other therapies, are expensive, and need additional oestrogens to prevent bone loss and menopausal symptoms, practice guidelines advise against the use of GnRH analogues for most women with hirsutism (Escobar-Morreale 2012; Martin 2008).

Glucocorticoids

Glucocorticoids are sometimes used in cases of non-classic congenital adrenal hyperplasia, which are not included within the scope of our review. They suppress adrenocorticotropic hormone-dependent adrenal androgen synthesis (Escobar-Morreale 2012; Lumachi 2010; Martin 2008). Well known side effects are weight gain, osteoporosis, and adrenal suppression.

Miscellaneous treatment options

There are a number of reasons for the apparent effectiveness of the following treatment options. Spearmint tea has been shown to have antiandrogenic properties (Grant 2010); statins reduce theca cell androgen production (Banaszewska 2011); ovary resection reduces serum testosterone (Ashrafinia 2009); inositol might have a positive effect on insulin resistance and additional lowering of serum testosterone levels (Ciotta 2012B); and cimetidine is a weak androgen receptor antagonist (Lissak 1989). Bromocriptine is a dopamine agonist and it is suggested that women with PCOS have lower LH secretions due to a deficiency in hypothalamic dopamine, which may lead to an excess in ovarian androgen production (Murdoch 1987). Sibutramine is an anti-obesity drug and, by improving weight loss, SHBG increases and free testosterone decreases (Sabuncu 2003). Clomiphene is considered to improve hormonal abnormalities in women with PCOS and thus might also have a beneficial effect on hirsutism (Roth 2012). Electro-acupuncture might reduce testosterone levels (Jedel 2011).

Why it is important to do this review

Hirsutism is a common and distressing disorder, which can have a major impact on the quality of life of an individual. There are a wide range of treatment options, but it is not clear which are the most effective, and many of these interventions may have important and undesirable side effects.

Several previous Cochrane reviews covered certain aspects of this review (Brown 2009; Costello 2007; van der Spuy 2003), but we will now incorporate these aspects into this review. This review is

needed to provide reliable decision-making information to clinicians and hirsute women about the evidence of effectiveness and safety of available treatments, and it will be the basis for recommendations for future research. Treatment with laser or photoepilation, which are often used to treat hirsutism, are covered in another Cochrane review (Haedersdal 2006).

We published the plans for this review as a protocol, 'Interventions for hirsutism excluding laser and photoepilation therapy', (van Zuuren 2013).

OBJECTIVES

To assess the effects of interventions (except laser and light-based therapies alone) for hirsutism.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included studies that considered the following participants: hirsute women of any age or ethnic background, women with polycystic ovary syndrome, idiopathic hirsutism, and idiopathic hyperandrogenism.

We excluded participants if their hirsutism was caused by or related to androgen-producing adrenal or ovary tumours, 21-hydroxylase-deficient non-classic adrenal hyperplasia, 21-hydroxylase classic adrenal hyperplasia, hyperprolactinaemia, Cushing's syndrome, drug-related hyperandrogenism, or acromegaly.

If studies included women from both of these groups, we only included those women that matched our inclusion criteria if separate data were available.

Types of interventions

We included any intervention alone or in combination versus active treatment, no treatment, or placebo, i.e. we included any oral and topical medications, lifestyle measures, or cosmetic treatment options, but we excluded light-based therapies and lasers alone as these are covered by another Cochrane review (Haedersdal 2006).

Types of outcome measures

We did not consider these prespecified outcomes as criteria for including studies in this review, but they are a representative list of the outcomes of interest within whichever studies were included. See section 5.1.2 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Primary outcomes

1. Participant-reported improvement of hirsutism measured at the end of the study or at other site-dependent and clinically important time points. Assessment would involve using a recognised or validated rating scale (e.g. visual analogue scale (VAS) and Likert scale).
2. Change in health-related quality of life (HRQOL) assessed using any validated or recognised quality of life instrument at the end of the study.
3. Proportion of participants who reported an adverse event throughout the study period. We reported individual serious adverse events separately.

We evaluated all **p**atient **r**eported **o**utcomes (PROs) against the 'Checklist for describing and assessing PROs in Clinical Trials' (see Chapter 17.6.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Secondary outcomes

1. Clinician's assessment of improvement of hirsutism with a standardised and validated scoring system (e.g. Ferriman-Gallwey score), or assessment of hair diameter, rate of growth, and length of hair at the end of the study.
2. Change in serum androgen levels (e.g. total testosterone, free testosterone, dehydroepiandrosterone, androstenedione, dihydrotestosterone) and SHBG at the end of the study.
3. Change in BMI at the end of the study.
4. Improvement of other clinical signs of hyperandrogenism (e.g. acne, seborrhoea, female pattern hair loss, ovulatory dysfunction) at the end of the study.

Depending on the type of intervention and the body area involved, we considered short-term assessments as periods up to six months and long-term assessments as outcomes after six months. The length of the hair growth cycles and the rate of hair growth differ in different body areas (Olsen 1999); therefore, the duration of the interventions needs to exceed at least the span of the hair growth cycle of the body areas to be treated. See also 'Physiology of hair growth' under Description of the condition and Description of the intervention.

We produced a 'Summary of findings' (SoF) table of the following outcomes listed according to priority:

1. Participant-reported improvement of hirsutism
2. Change in HRQOL
3. Proportion of participants reporting an adverse event

4. Clinician's assessment of improvement of hirsutism
5. Change in serum androgen levels
6. Change in BMI
7. Improvement of other clinical signs of hyperandrogenism

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 11 June 2014:

- the Cochrane Skin Group Specialised Register using the following terms: hirsut* or frazonism or (unwanted and hair and growth) or (excess* and terminal and hair*);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 6) using the search strategy in Appendix 1;
- MEDLINE via OVID (from 1946) using the strategy in Appendix 2; and
- EMBASE via OVID (from 1974) using the strategy in Appendix 3.

Trials registers

We searched the following trials registers on 14 June 2014 (EvZ and ZF) using the following search terms: 'hirsutism', 'hyperandrogenism', and 'unwanted hair growth'.

- the *meta*Register of Controlled Trials (www.controlled-trials.com);
- the US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Searching other resources

References from published studies

We (EvZ and ZF) examined the bibliographies of the included and excluded studies for further references to potentially eligible randomised controlled trials.

Correspondence

We (EvZ and ZF) contacted trial investigators and asked them to provide missing data or clarify study details.

Adverse effects

We did not conduct a separate search for adverse effects of interventions for hirsutism. However, we examined data on adverse effects from the included studies that were identified.

Data collection and analysis

Some parts of the methods section of this review use text that was originally published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), as well as a number of other Cochrane reviews variously co-authored by EvZ, ZF, and BC.

Selection of studies

Two authors (EvZ and ZF) independently assessed the abstracts of studies resulting from the searches. We obtained full copies of all relevant and potentially relevant studies, those appearing to have met the inclusion criteria, or for which there was insufficient information in the title and abstract to make a clear decision on eligibility. We assessed the full-text papers independently and resolved any disagreement on the eligibility of included studies through discussion and consensus. We excluded those records that did not meet the inclusion criteria, and we noted the reasons for their exclusion in the 'Characteristics of excluded studies' section of the review.

Data extraction and management

Two authors (EvZ and ZF) independently collected study details and outcomes data using a predetermined form designed for this purpose. We entered study details into the 'Characteristics of included studies' table in Review Manager (RevMan 2014). The authors only included data if there was an independently reached consensus.

If reported, we extracted the following details.

(a) Trial methods - method of sequence generation and concealment of allocation sequence; masking of participants, trialists, and outcome assessors; exclusion of participants after randomisation; proportion of and reasons for losses to follow-up.

(b) Participants - country and study setting; sample size; age; ethnicity; inclusion and exclusion criteria.

(c) Intervention - type; concentration, dose, and frequency; route of administration; duration of intervention and follow-up.

(d) Control - type; duration of intervention and follow-up.

(e) Outcomes - primary and secondary outcomes as specified in the 'Types of outcome measures' section of this review. We determined

the outcome as short-term if it was taken between completion of the intervention and up to one month of follow-up; medium-term between one month but less than six months' follow-up; and long-term for six or more months' follow-up.

If stated, we recorded the sources of funding of the included studies.

Assessment of risk of bias in included studies

Two review authors (EvZ and ZF) assessed the risk of bias of the selected studies independently using The Cochrane Collaboration's tool for assessing risk of bias as described in Chapter 8, section 8.5, in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We compared the evaluations and discussed and resolved any inconsistencies between the review authors.

We assessed the following domains as 'low risk of bias', 'unclear' (uncertain risk of bias), or 'high risk of bias':

1. sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcomes assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We reported these assessments for each individual study in the 'Risk of bias' tables.

We categorised and reported the overall risk of bias of each of the included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

We presented continuous outcomes on the original scale as reported in each individual study. If similar outcomes were reported using different scales, we converted these to standardised mean differences (SMD). We presented either mean differences (MD) or SMD with their associated standard deviation in parenthesis.

We presented dichotomous outcomes as risk ratios (RR) and, if found significant, we converted them to either: the number of patients needed to treat to find one additional beneficial outcome (NNTB); or the number needed to treat to find one additional harmful outcome (NNTH) (Newcombe 1998).

We reported all outcomes' data with their associated 95% confidence intervals (CI) and analysed them in RevMan 5 (RevMan 2014) according to a random-effects model using the Mantel-Haenszel test for dichotomous outcomes and inverse variance for continuous outcomes (unless stated otherwise). See section 9.4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

Cross-over trials

Unit of analysis issues can arise in studies where participants have been randomised to multiple treatments in multiple periods or where there has been an inadequate wash-out period. We analysed these data based on the advice provided in section 16.4.4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the carry-over and period effects descriptively, and if there was evidence of minimal impact and there were adequate data, we carried out a paired analysis.

Studies with multiple treatment groups

Studies that are reported with multiple treatment groups have the potential for participant data to contribute to multiple comparisons. We assessed the treatments and determined which were relevant to our review then allocated the non-intervention participants as the 'shared' group. We split the 'shared' group equally into the number of comparisons made, as discussed in section 16.5.4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Within-patient studies

Unit of analysis issues can arise in studies where participants have been randomised to multiple treatments on different parts of their body. We analysed these data based on the advice provided in sections 9.3.8 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the potential risk of treatment contamination and general change in the control group descriptively and, if there was little suggestion of these and there was adequate information, we carried out a paired analysis. For paired analysis pooled comparisons, we have calculated the natural logarithm of the marginal odds ratio and variance and used these as treatment effects in a generic inverse variance model to compare interventions with a random-effects model (Stedman 2011).

Dealing with missing data

If data were missing from trials that were less than 10 years old, we tried wherever possible to contact the investigators or sponsors of these studies. We re-analysed data according to the intention-to-treat (ITT) principle whenever possible. For dichotomous outcomes, if authors had conducted a per-protocol analysis, we carried out an ITT analysis with imputation setting the missing data to their baseline values, checking the degree of imbalance of drop-

out between the arms to determine the potential impact of bias (section 16.2.2 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If no suitable value could be carried forward (e.g. adverse events), we conducted a complete case analysis. For continuous outcomes, we carried out a per-protocol analysis in place of an ITT analysis.

Where change from baseline scores are not presented, but baseline and follow-up data are summarised, the change from baseline scores have been estimated assuming a common correlation of structure of 0.8 (section 16.1.3.2 in the *Cochrane Handbook for Systematic Reviews of Interventions)* (Higgins 2011). In studies where the standard deviation has been summarised at baseline (or may be estimated at baseline) but not follow-up, the standard deviation has been assumed to remain unchanged at follow-up. Where only medians were presented with ranges, the mean was estimated by the median, and the variance estimated using the range and the number of observations (Hozo 2005).

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the studies and the similarity between the types of participants and the interventions. We assessed the degree of heterogeneity between the studies using the I^2 statistic. We reported heterogeneity as important and at least moderate to substantial if the I^2 statistic > 60% (Higgins 2011). If this could be explained by clinical reasoning and a coherent argument could be made for combining the studies, we entered these into a meta-analysis. In cases where the heterogeneity could not be adequately explained, we did not pool the data.

Assessment of reporting biases

Our assessments of reporting bias followed the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in section 10.4.3.1 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed these for primary and secondary outcomes for meta-analysis when we included a minimum number of studies, to allow a reasonable estimate of the effect of intervention (nominally nine studies). We only presented funnel plots where there was some evidence of asymmetry in the plots. We explored possible sources of asymmetry with an additional sensitivity analysis.

Data synthesis

Two review authors (EvZ and ZF) analysed the data in RevMan (RevMan 2014) and reported them in accordance with the advice in Chapter 9 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We carried out a random-effects meta-analysis if we were able to identify an adequate number of studies (n $\geq$ three) that investigated similar interventions and reporting data that exhibited not more than moderate heterogeneity (Treadwell 2006).

Subgroup analysis and investigation of heterogeneity

We considered the following subgroup analyses:

- ethnic background;
- severity of the hirsutism;
- hyperandrogenism;
- cause of hirsutism;
- premenopausal and postmenopausal status; or
- timing of outcome.

However, we did not find enough studies to carry out any subgroup analysis.

Sensitivity analysis

We conducted sensitivity analyses, but did not report these since the impact of the assumptions that we made did not influence the interpretation of any of the findings. The two assumptions that we made were: using a fixed correlation structure when computing the change from baseline standard deviation (r = 0.8) and using a random-effects pooling method.

RESULTS

Description of studies

See 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Results of the search

Our searches retrieved 1118 references to studies. Searching of the trial registers identified 14 ongoing studies, and the bibliographies of the included and excluded studies provided an additional 45 potentially eligible studies. We identified a total of 1177 references for evaluation.

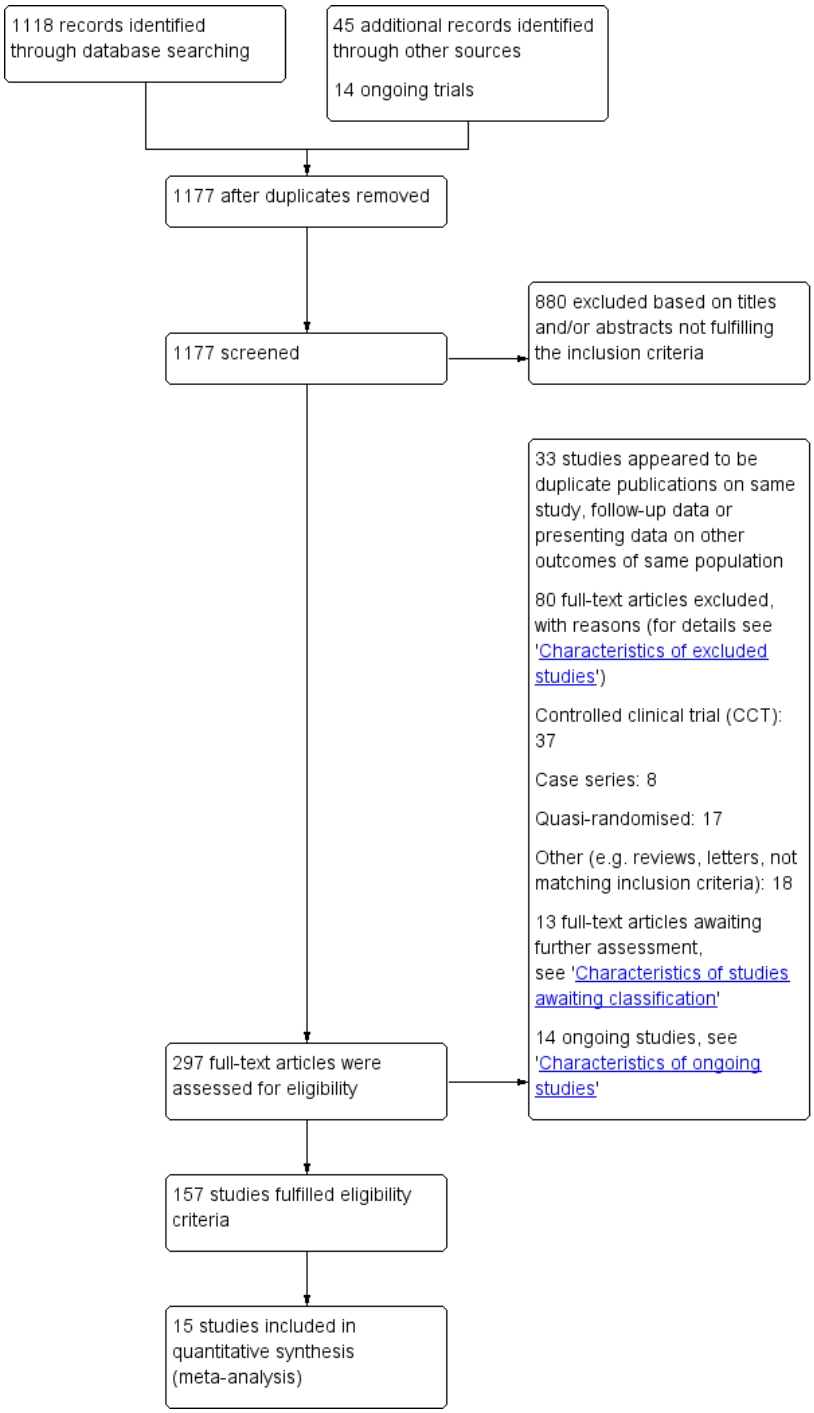
After the removal of duplicates and examination of the titles and abstracts, we excluded 880 references from the review. We then subjected the full-text copies of the remaining 297 studies to further evaluation. A number of studies (18) were not published in the English language; Farsi (one) (Esmaeilzadeh 2010), Spanish (two) (Devoto 2000; Devoto 2004), German (six) (Erdmann 1994; Grund 1975; Hahn 2004; Lachnit-Fixson 1977; Lee 2000; Weiss 2007), Italian (four) (Falsetti 1997B; Farina 2006; Le Donne 2012; Paggi 1981), Danish (two) (Nielsen 1985; Pedersen 1985), French (one) (Pugeat 1991), Slovakian (one) (Visnovský 2010),

and Polish (one) (Baranowska 1983), but these were all translated prior to assessment for eligibility.

Out of the 297 studies, 33 appeared to be duplicate publications and are listed under the primary references. We excluded 80 with reasons (see 'Characteristics of excluded studies'), 13 studies are awaiting further assessment (see 'Characteristics of studies awaiting classification'), and 14 are ongoing trials (see 'Characteristics of ongoing studies' section) leaving a total of 157 included studies (see 'Characteristics of included studies').

For further details see the 'Study flow diagram' (Figure 4).

Figure 4. Study flow diagram.



Included studies

The review included 157 studies comprising 10,550 women (see the 'Characteristics of included studies' section).

Characteristics of the trial setting and methods

All of the studies were randomised controlled trials, 36 included a placebo arm, 112 had an active control treatment arm, and nine studies included both arms. Most (100) of the studies were conducted after the year 2000. The majority (138) were single-centre studies, and the remainder (19) were multi-centre studies. The studies were conducted in Europe (97), in the USA/Canada (21), in Mid and South-America (10), in Asia (20), in Africa (three), in Australia (four), and two on different continents.

Characteristics of the participants

The number of participants included in the individual studies varied widely, from 8 to 596, with between 30 and 80 representing the most common sample size. The mean age of the participants in the individual studies ranged from 15 to 46 years, with an overall mean age of 25.4 years.

Characteristics of the interventions

A wide range of interventions were evaluated, which we have categorised into nine groups (see Table 2). The 157 studies covered 165 comparisons, most of which included an active control arm. A total of 48 studies did not report any usable data (see Table 3), reducing the total number of comparisons that provided usable data to 133. Duration of the intervention varied from 10 days to two years, but in the majority of studies this was between six and 12 (mean 7.9) months. Although a study duration of 10 days or a month may be too short a period to observe a benefit on hirsutism, these studies have been included as a short study duration was not an exclusion criterion (Cedeno 1990; Elnashar 2006; Grant 2010).

Characteristics of the outcome measures

Very few of the included studies addressed our primary outcomes. Only 26/157 studies reported data on participant-reported improvement of hirsutism. In 11 of these this outcome was assessed using a Likert scale (three- to six-point), in one a visual analogue scale (VAS) (Harborne 2003), and one study used an alternative analogue scale (Barth 1991). The trialists in one study utilised an outcome measure (ESTEEM), which they had modified from the Bother Assessment in Skin Conditions (BASC) instrument, but provided very limited information on how the modified assessment tool was subsequently tested and validated (Jackson 2007). Questionnaires were used in the remaining studies but the reports provided very limited details about how these were used to assess outcomes.

Three studies reported change in health-related quality of life (HRQOL) (Consoli 1994; Grant 2010; Ladson 2011). The generic Dermatology Quality of Life Index was used in one of these studies (Grant 2010), and the disease-specific PCOS quality of life survey was used in Ladson 2011. An 11-item questionnaire with each question rated on a four-point Likert scale was used in Consoli 1994.

Less than half of the studies (63/157) reported on adverse events and as the treatments varied, so did the accompanying adverse events. None of the instruments used to assess our primary outcomes, which were all PROs, met all the recommended criteria based on the 'Checklist for describing and assessing PROs in Clinical Trials' (see Chapter 17.6.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The majority of studies (135/157) reported clinician's assessment of improvement of hirsutism, which was predominantly assessed using the Ferriman-Gallwey score. Change in androgen levels was measured in most of the studies (140/157), while BMI and improvement of other clinical signs of hyperandrogenism were evaluated in 49/157 and 56/157 of studies respectively.

Excluded studies

We excluded 80 studies from this review only after evaluation of their full-text copies. We excluded all of these largely on the basis that they were non-randomised trials (see 'Characteristics of excluded studies'). Although the titles of 17 studies appeared to indicate that these were randomised trials, further examination of the full-text versions of these reports revealed that they were in fact quasi-randomised (allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation).

Risk of bias in included studies

We assessed each of the included studies for risk of bias and reported the judgements for the individual domains in the 'Risk of bias' table associated with each study. We have also presented these in the 'Risk of bias' graph in Figure 5 and the 'Risk of bias' summary in Figure 6.

Figure 5. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

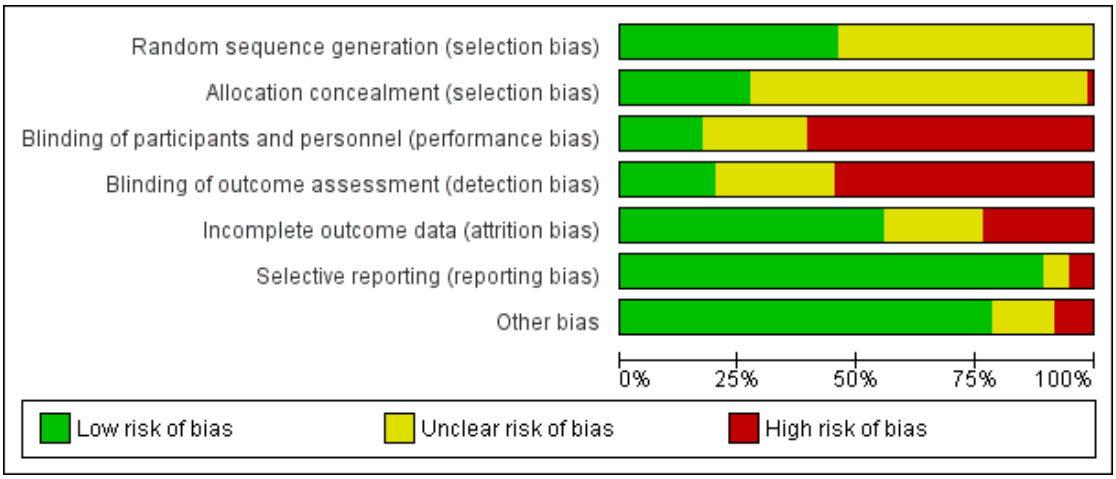
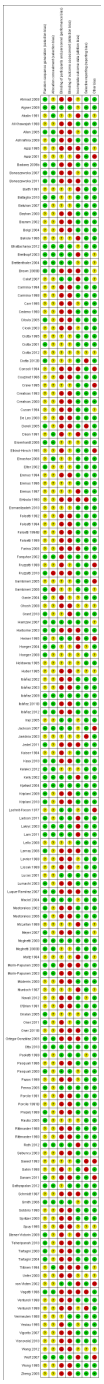


Figure 6. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Only four of the studies met all of the criteria across all of the domains in The Cochrane Collaboration's tool for assessing the risk of bias, and therefore we considered these studies to be at 'low risk of bias' (plausible bias unlikely to seriously alter the results) (Ibáñez 2009; Kjøtrød 2004; Moghetti 2000; Otta 2010). We considered the majority of the studies (123/157) to be at 'high risk of bias' (plausible bias that seriously weakens confidence in the results) because one or more domains received a judgement of high risk. Of all the 157 studies, 96 were not blinded, which represented the most frequent potential source of bias. We categorised the remaining studies (30/157) as 'unclear risk of bias' (plausible bias that raises some doubt about the results) because we assessed one or more criteria as unclear. For these and further details, see the 'Risk of bias' tables in the 'Characteristics of included studies' section.

Allocation

The methods used to generate the allocation sequence and how the sequence was concealed, such that participants and investigators enrolling participants could not foresee the upcoming assignment, are the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995).

Sequence generation

In 87 out of the 157 trials in this review the method of sequence generation was not described at all or was at best unclear. In the remainder (70) the method used to generate the allocation sequence was described in sufficient detail; therefore, we judged this domain as low risk of bias for these studies.

Allocation concealment

The method used to conceal the allocation sequence was not reported in 111 out of the 157 trials, which received a judgement of unclear risk of bias for this domain. In 44 studies allocation concealment was ensured by central allocation, was pharmacy-controlled, or was achieved through the use of serially numbered, opaque envelopes. We judged the risk of bias for this domain to be high in two studies because the investigators had access to the random-number table and it was likely that allocation could be foreseen (Fruzzetti 2010; Gambineri 2006).

Blinding

The majority of studies (96) were open-label design and therefore the outcome or outcome measurement was likely to be influenced by lack of blinding and, thus, we judged the domain for performance bias as at 'high risk'. For two studies, we did not consider the open-label design to have any significant influence on the outcome assessment (detection bias) as both outcomes, i.e. ovulation and serum tests, are unlikely to be influenced by the lack of blinding (Farquhar 2002; Vexiau 1995). The measures used to blind study participants and personnel from knowledge of which intervention a participant received were described in sufficient detail in only 27 of the studies. Blinding was achieved largely through the use of either identical pre-labelled bottles or tubes, or with the use of similar packaging and the use of identical pills, tablets, or capsules. In the remaining 34 studies the method used to blind participants, healthcare providers, or outcome assessors was not described at all or not in sufficient detail, and therefore we judged the risk of bias as 'unclear' for this domain.

Incomplete outcome data

In slightly more than half (88) of the studies, incomplete outcome data appear to have been adequately addressed and the losses were reasonably well-balanced across intervention groups, with similar reasons for missing data across the groups. However, we gave a judgement of high risk of bias for 36 studies mainly due to substantial (> 20%) drop-out rates and subsequent per-protocol data analysis. We judged the risk of bias in the remaining 33 studies to be unclear for this domain.

Selective reporting

Based on the information in the methods section of the reports, 141 of the 157 studies appear to have reported all prespecified outcomes and we therefore judged them to be free of selective reporting. We judged the 16 remaining studies to be unclear (nine) and high (seven) risk of bias. Six of these studies were abstracts or posters to conference proceedings, which provided insufficient information to make a clear judgement for this domain (Ciotta 2012; Ghosh 2008; Huber 1985; Spuy 1995; Unfer 2000; Wang 2012). There were 29 duplicate publications of included studies, which we excluded as they would lead to overestimation of intervention effects (multiple publication bias) (see Figure 4).

Other potential sources of bias

We judged this domain as 'low risk of bias' in most of the studies (125/157). In 13/157 studies we judged this domain as at high risk for several reasons, i.e. that the investigators were employed by the pharmaceutical company of the drug under research and a potential risk of bias could not be excluded, or if there was serious baseline imbalance. In situations where the report provided insufficient information on the extent of support provided by the pharmaceutical company or if the lack of detail in the report did not allow us to assess adequately the presence of other possible sources of bias, we judged the domain as 'unclear' (19/157).

Effects of interventions

See: **Summary of findings for the main comparison** Ethinyl estradiol 35 μg + cyproterone acetate 2 mg compared to ethinyl estradiol 30 μg + desogestrel 0.15 mg for hirsutism; **Summary of findings 2** Flutamide 250 mg b.i.d. compared to placebo for hirsutism; **Summary of findings 3** Flutamide 250 mg once to b.i.d. compared to spironolactone 100 mg for hirsutism; **Summary of findings 4** Spironolactone 100 mg compared to placebo for hirsutism; **Summary of findings 5** Finasteride 5 mg to 7.5 mg compared to placebo for hirsutism; **Summary of findings 6** Metformin 500 mg to 2550 mg per day compared to placebo for hirsutism; **Summary of findings 7** Finasteride 5 mg compared to spironolactone 100 mg for hirsutism; **Summary of findings 8** Flutamide 250 mg once to twice daily compared to metformin 1275 mg to 1700 mg per day for hirsutism; **Summary of findings 9** Finasteride 5 mg compared to flutamide 250 mg once to b.i.d. for hirsutism

Less than one-third (48/157) of the included studies, which covered 32 comparisons, provided no usable or retrievable data and did not contribute further to the results of this review (see Table 3). The main reasons why data could not be used were: no separate data reported on hirsute women, the very limited data available in abstracts to conference proceedings, and losses to follow-up of participants with drop-out rates in excess of 40%.

The minimal important difference (MID) represents the between-groups criterion that needs to be met or exceeded in order for study results to be considered clinically meaningful. As yet the MID for the Ferriman-Gallwey score has not been established, and therefore in order that we provide meaningful data based on the clinician's assessments of these scores we indicate, where appropriate, if the changes from baseline or the mean differences between groups for these assessments were clinically important. To this extent a change in Ferriman-Gallwey score in excess of 7 from baseline is generally considered to be a clinically important change as indeed is a mean difference of at least 7 in Ferriman-Gallwey score between groups (see Figure 3). Degrees of hirsutism and the matching assessment scores correlate poorly with androgen levels and although we report these changes in androgen levels and whether they were statistically significant, we only indicate these as being clinically important if they reflect corresponding changes in hirsutism score.

None of the studies evaluated cosmetic measures such as depilatory creams, bleaching, waxing, or electrolysis, while laser and photoepilation were included in another Cochrane review (Haedersdal 2006).

We have addressed our prespecified outcomes under the following intervention headings

- Lifestyle modification (comparisons 1 to 2)
- Topical treatments (comparisons 3 to 6)
- Oral contraceptive pills (comparisons 7 to 20)
- Antiandrogens (comparisons 21 to 24)
- 5α reductase inhibitors (comparisons 25 to 29)
- Insulin-sensitising agents (comparisons 30 to 37)
- Combined treatments (comparisons 38 to 101)
- Other treatment comparisons (comparisons 102 to 133)

We did not provide detailed data for changes in androgen levels when these were not statistically significant or not clinically meaningful with respect to improvement or lack of improvement in hirsutism, but these changes in levels are reported in the 'Changes in androgen levels' tables (see Data and analyses). Baseline values for the individual studies are reported in the 'Characteristics of included studies' and will not be repeated to avoid duplication of text.

Nine 'Summary of findings' tables for comparisons that were considered to be important by the review authors, or where data could be pooled for various outcomes, summarise the quality of the body of evidence for each of these comparisons (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8; Summary of findings 9).

Lifestyle modification

(1) Exercise three times a week for 30 minutes versus no exercise over three to four months

This intervention and comparison was examined in two studies assessed at 'high risk of bias' (Jedel 2011; Vigorito 2007): a three-armed study of 51 women with polycystic ovary syndrome (PCOS) (Jedel 2011) (see comparison 128 and 129) and a further study, which included 90 overweight women with PCOS (Vigorito 2007). The entire PCOS study population received general dietary and behavioural advice but this did not include a structured caloric restriction programme.

Primary outcomes

Participant-reported improvement of hirsutism

Change in health-related quality of life (HRQOL)

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event

This outcome was not assessed in Jedel 2011 and although this was not a prespecified outcome in Vigorito 2007, the trialists indicated that no adverse events occurred during the training sessions.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

In Jedel 2011 both groups showed minimal increases in the mean Ferriman-Gallwey score of 0.72 (3.54) in the exercise group and 1.40 (3.66) in the no intervention group (mean difference (MD) -0.68, 95% confidence interval (CI) -3.16 to 1.80; P value = 0.59). In Vigorito 2007 there was a slight reduction in the mean Ferriman-Gallwey score in the exercise group of 0.40 (2.12) as compared to a non-significant increase of 0.20 (2.10) in the control group (MD -0.60, 95% CI -1.47 to 0.27; P value = 0.18).

Change in serum androgen levels

There were minimal changes from baseline in the serum androgen levels in both groups and with minimal differences between the groups (see Analysis 1.1).

Change in body mass index (BMI)

Minimal increases in mean BMI were reported in both groups in Jedel 2011. In the exercise group there was an increase of 0.01 kg/m² (0.70) and in the control group an increase of 0.11 kg/m² (0.63) (MD -0.10 kg/m², 95% CI -0.55 to 0.35; P value = 0.66). In Vigorito 2007 there was a slight improvement, illustrated by a decreased BMI in the exercise group with a mean change of 1.30 kg/m² (1.83) versus a smaller change of 0.10 kg/m² (2.14) in the control group (MD -1.20 kg/m², 95% CI -2.02 to -0.38; P value = 0.004). Although this difference is statistically significant it did not appear to have any impact on the severity of the hirsutism.

Improvement of other clinical signs of hyperandrogenism

The investigators in Jedel 2011 stated that "menstrual frequency improved more in the physical exercise group than in the no active intervention group" (authors state P value = 0.014), but data were only reported in a graph plot. Between-group differences for the change from baseline to week 16 were determined by Kruskal-Wallis test followed by Mann-Whitney U-test. This outcome was not assessed in Vigorito 2007.

(2) Lifestyle modification (+ placebo tablets) versus placebo tablets for 24 weeks to 12 months

One study, which included four treatment arms, addressed the effect of a lifestyle modification programme (+ placebo tablets) that included nutrition, behaviour, and physical activity versus placebo alone (Hoeger 2004). The study had a high drop-out rate of almost 40%. The other possible comparisons in this study are addressed under comparisons 32, 38 to 41. Participants received a personally tailored diet aiming for a 500 to 1000 calorie deficit per day and every participant was recommended to undertake 150 minutes of exercise per week. These investigators also conducted a four-armed study several years later (Hoeger 2008 study 1), which had a shorter duration of 24 weeks (see also comparison 17, 32, 103, 105, and 112).

Primary outcomes

Participant-reported improvement of hirsutism

Change in health-related quality of life (HRQOL)

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event

This outcome was inadequately addressed in Hoeger 2004, with no side effects listed per treatment arm, and only reported as generalised comments covering the four treatment arms. This outcome was not addressed in Hoeger 2008 (study 1).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The data we report in Hoeger 2004 had to be estimated from a box-and-whisker plot. The estimated mean change in the modified Ferriman-Gallwey score in the six participants in the lifestyle modification programme group showed a reduction of 3.0 (4.64) compared to an increase of 0.6 (2.58) in the seven participants in the control group (MD -3.60, 95% CI -7.78 to 0.58; P value = 0.09), which was not a statistically significant difference. The effects reported in Hoeger 2008 (study 1) were smaller and most probably due to the shorter study duration. In this study the mean Ferriman-Gallwey score reduced by 1.00 (1.24) in the lifestyle modification group and by 0.90 (3.25) in the placebo group (MD -0.10, 95% CI -2.29 to 2.09; P value = 0.93).

Change in serum androgen levels

There were no clinically important differences in testosterone or sex hormone-binding globulin (SHBG) levels between the two groups associated with improvements in hirsutism (see Analysis 2.1).

Change in BMI

This outcome was not assessed in Hoeger 2004, whereas in Hoeger 2008 (study 1) the mean BMI reduced by 2.90 kg/m² (4.94) in the lifestyle modification group and in the placebo group by 0.60 kg/m² (4.57) (MD -2.30 kg/m², 95% CI -6.74 to 2.14; P value = 0.31).

Improvement of other clinical signs of hyperandrogenism

No precise data were reported but the authors stated in both studies that, "overall, no significant differences were demonstrated in ovulatory events between treatment groups and the placebo group".

Topical treatments

(3) Eflornithine HCl 13.9% cream versus vehicle, each applied twice daily for 24 weeks

Two studies, Jackson 2007 and Wolf 2007, compared and reported data for these interventions but assessed different outcomes. The numbers of participants completing the study are not consistently reported in the two studies (see Notes in 'Characteristics of included studies' and in 'Contact with investigators' under Additional tables).

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was not assessed.

Change in health-related quality of life (HRQOL)

In Jackson 2007 the investigators used the ESTEEM instrument for assessing the level of 'bother' caused by hirsutism and the changes brought on by the treatment. Eflornithine was shown to be more effective than vehicle when assessed for this single outcome ('overall bother'), which was one of the six patient-reported outcomes (PROs) integral to the ESTEEM instrument (see Notes in 'Characteristics of included studies' and Caro 1996). With regard to being "bothered by facial hair" or "overall bother", the mean decrease on the visual analogue scale (VAS) was 30.7 (32.03) after 24 weeks in the 355 participants using eflornithine cream compared to a decrease of 14.4 (21.04) in the 173 participants in the vehicle group (MD 16.30, 95% CI 11.72 to 20.88; P value < 0.001).

Proportion of participants who reported an adverse event

There was inconsistency in reporting of the number of participants in both studies, however in Wolf 2007 182/395 (46%) of the participants reported adverse events versus 80/201 (40%) of those in the vehicle group, indicating a difference that was not statistically significant (risk ratio (RR) 1.16, 95% CI 0.95 to 1.41; P value = 0.15). The most important adverse effects were acne and pseudofolliculitis barbae, which accounted for around 37% of the participants in both treatment groups. The only side effects that occurred were burning, stinging, and tingling, which were reported more frequently in the eflornithine group (14.2%) compared to the vehicle group (5%). Additional adverse effects that were reported in both groups were pruritus, dry skin, alopecia, erythema, irritation, dermatitis, and rash.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

Physician's global assessments were dichotomised by the investigators in Wolf 2007 into 'success' (clear or almost clear or marked improvement) and 'failure' (improved or no improvement or worse). In the eflornithine group 126/395 (32%) of the participants were considered a clinical success compared to 18/201 (9%) of the participants in the vehicle group (RR 3.56, 95% CI 2.24 to 5.66; P value < 0.001, number needed to treat for an additional beneficial outcome (NNTB) = 5, 95% CI 4 to 7), which is a clinically important difference.

Video analysis confirmed a reduction in hair mass of 26% in the eflornithine group versus 5% in the vehicle group, as well as a reduction in hair length of 23% versus 4% respectively (authors stated P value = 0.016).

Change in serum androgen levels

Change in BMI

Improvement of other clinical signs of hyperandrogenism

None of the above three outcomes were assessed.

(4) Long-pulsed alexandrite laser + eflornithine 13.9% cream twice daily versus long-pulsed alexandrite laser + vehicle cream twice daily for six to eight months

Two studies, both of which were within-participant comparisons, evaluated the effects of eflornithine cream as add-on therapy to laser therapy for facial hirsutism (Hamzavi 2007; Smith 2006). As both treatment arms in the two studies included laser therapy and the treatment under investigation was eflornithine cream, we included these studies in our review. Study duration was six months in Hamzavi 2007 and 34 weeks in Smith 2006. Insufficient data were reported in both studies to permit calculation of marginal odds ratios (OR) for any of the outcomes.

Primary outcomes

Participant-reported improvement of hirsutism

In Hamzavi 2007, 13/33 (39.3%) participants considered that the side treated with eflornithine cream looked 'better', while 18/33 (54.5%) noticed no difference but these included two participants who dropped out. The participants in Smith 2006 were generally more positive about the effects of eflornithine and 60% (32/54) of the 54 participants that finished the treatment preferred the eflornithine treated side compared to 20% (11/54). Ten out of the 64 (15.6%) participants did not complete the study.

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

The number of adverse events reported by participants varied markedly between the two studies. In Hamzavi 2007 4/33 participants reported an adverse event on the eflornithine treated side (mild discomfort (two), mild tingling (one), and transient hyperpigmentation (one)) and none were experienced on the sides of the face which received placebo (no meaningful OR could be calculated). In Smith 2006 a total of 40 adverse events were reported in 27/54 participants. On the eflornithine treated side 15 (23%) participants reported 23 adverse events, and on the vehicle treated side 12 (19%) participants reported 17 adverse events. Most of the adverse events (74%) in this study were considered to be mild. Acne developed on the eflornithine cream side in eight (13%) women and on the vehicle side in seven (11%) women, a difference which might reflect the composition of the vehicle. Herpes simplex reactivation developed on the eflornithine cream side in four (6%) women and on the vehicle side in two (3%) women.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

In Hamzavi 2007 the clinicians considered the eflornithine treated side to be 'clear or almost clear' in 29/33 of the participants versus 21/33 on the vehicle-treated side. In Smith 2006 the clinicians rated both treatments as being more or less equally effective, i.e. 65% to 70% of participants in both groups received a rating of 'marked improvement' or 'clear' for chin and upper lip. The data from both studies appear to indicate that the effect is mainly due to the laser treatment.

Change in serum androgen levels

Change in BMI

Improvement of other clinical signs of hyperandrogenism

None of the above three outcomes were assessed.

(5) Finasteride (0.25% or 0.5%) cream versus placebo, each applied twice daily for six months

Two studies reported usable data for these interventions (Iraji 2005; Lucas 2001). Both studies had a within-participant design, which included only eight participants in the 0.25% finasteride cream study (Lucas 2001), compared to 35 participants in the 0.5% finasteride cream study (Iraji 2005). The results as reported in the two studies were contradictory, there was no demonstrable reduction in the number of terminal hairs or hair thickness in the 0.5% finasteride cream study; whereas the study with the lower concentration (0.25%) reported a 'significant decrease'. Insufficient data were reported in both studies to permit calculation of marginal odds ratios (OR) for any of the outcomes. The investigators in Iraji 2005 indicated that 5/35 (14.3%) of the participants failed to complete the study because they did not "note any difference".

Primary outcomes

Participant-reported improvement of hirsutism

Six out of the eight participants in Lucas 2001 noted a considerably diminished hair growth rate as well as a decreased thickness of the hair on the side of the face treated with finasteride cream, whilst the remaining two reported no difference between the sides of the face. The investigators in Iraji 2005 reported that 25/35 of the participants "noted a considerable diminished rate of hair growth on both sides of the face, especially on the one side that they had guessed that side is medication". Five had a mildly diminished rate of hair growth and five indicated that they had not noticed any change.

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

Neither of the two studies reported any adverse events for either of the interventions.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The number of terminal hairs/cm² was assessed in both studies. In Iraji 2005 the mean change from baseline was -2.90 hairs/cm² (3.70) in the finasteride 0.5% cream group compared to -1.70 hairs/cm² (3.69) in the placebo group and the investigators stated that there was no statistically significant difference between the groups. In contrast, in the eight participants in Lucas 2001 the mean change from baseline was -12 hairs/cm² (23.74) for the finasteride 0.25% cream group and -3 hairs/cm² (23.74) for the vehicle group (the investigators stated that there was significantly 'decreased hair growth'). The mean change from baseline of hair thickness in Iraji 2005 was -0.80 μm (0.54) in the finasteride 0.5% group and -0.20 μm (0.52) in the placebo group, a difference which the investigators stated was not statistically significant. In Lucas 2001 no pretreatment data were reported other than that there was no statistically significant difference between the groups. The investigators concluded that after the treatments there was a significant difference between the groups as the thickness of the hairs was 3.11 μm (0.14) in the finasteride 0.25% group versus 4.33 μm (0.20) (authors state P value < 0.001 (paired t-test)).

Change in serum androgen levels

These outcomes were not assessed in Iraji 2005, and although no data were reported in Lucas 2001, the investigators stated that the androgen levels did not change significantly during the study.

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(6) Fennel 1% cream versus fennel 2% cream versus vehicle each applied twice daily for 24 weeks

A single study assessed at high risk of bias reported data for these interventions (Javidnia 2003).

Primary outcomes

Participant-reported improvement of hirsutism

Although 'patient satisfaction' was an outcome that was prespecified in the methods section of this study, no data were reported (see 'Risk of bias' assessment under 'Characteristics of included studies' for this study (Javidnia 2003)).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

This outcome was not assessed, however the investigators indicated that there were no adverse events.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean value of the reduction in hair diameter was 7.8% (3.7) for the fennel 1% cream group (N = 11), 18.3% (8.3) for the fennel 2% cream group (N = 15), and 0.5% (2.1) in the vehicle group (N = 12). Although hair growth rate was one of the prespecified outcomes for the trial it was not reported by the investigators.

Change in serum androgen levels

Change in BMI

Improvement of other clinical signs of hyperandrogenism

None of the above three outcomes were assessed.

Oral contraceptive pills

(7) Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + drospirenone 3 mg for 12 months

Two studies provided usable data for this comparison (Batukan 2007; Bhattacharya 2012). Bhattacharya 2012 had three treatment arms and the other comparisons are listed below (comparison 8 and 9).

Primary outcomes

Participant-reported improvement of hirsutism

Change in health-related quality of life (HRQOL)

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event

This outcome was not assessed in Batukan 2007, but in Bhattacharya 2012 two participants in each group (50) experienced a side effect (RR 1.02, 95% CI 0.15 to 6.98; P value = 0.99).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean Ferriman-Gallwey score decreased by 12 in both groups in Batukan 2007. The mean reduction in the ethinyl estradiol (EE) + cyproterone acetate (CPA) group was 12 (1.07) and in the EE + drospirenone group 12 (1.14), which is a clinically meaningful change, however the mean difference between the two groups was 0.0 (95% CI -0.45 to 0.45; P value = 1.00). Both therapies appeared to be highly effective in the reduction of terminal hairs. In Bhattacharya 2012 the reduction in the modified Ferriman-Gallwey score was lower; 5.29 (5.88) in the EE + CPA group, which was less pronounced than in Batukan 2007, while in the EE + drospirenone group the reduction was just 2.12 (6.58) (MD -3.17, 95% CI -5.61 to -0.73; P value = 0.01). Although this difference was statistically significant, it is not clinically important.

Change in serum androgen levels

There were minimal changes from baseline in the serum androgen levels in both groups and minimal differences between the groups, which were unlikely to be clinically important with respect to any difference in the improvement of hirsutism and, except for the difference in SHBG and androstenedione in Batukan 2007, were also not statistically significant (see Analysis 3.1).

Change in BMI

This outcome was only assessed in Bhattacharya 2012, which reported a reduction in BMI of 0.59 kg/m² (4.76) in the EE + CPA group and an increase of 0.11 kg/m² (5.54) in the EE + drospirenone group (MD -0.70 kg/m², 95% CI -2.72 to 1.32; P value = 0.50).

Improvement of other clinical signs of hyperandrogenism

Only Bhattacharya 2012 addressed this outcome but it was unclear in the report which type of instrument was used to measure the change in acne severity, and therefore accurate interpretation of the outcome data was not feasible. The investigators reported a reduction in acne score of 1.52 (1.25) in the EE + CPA group and 1.42 (1.27) in the EE + drospirenone group with no statistically significant difference between the groups (MD -0.10, 95% CI -0.59 to 0.39; P value = 0.69).

(8) Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg for 12 months to two years

This comparison was addressed by four studies (Bhattacharya 2012; Mastorakos 2002; Mastorakos 2006; Porcile 1991), but the duration of Porcile 1991 was one year longer than the others. One of these was a three-armed study (Bhattacharya 2012), and the data are also reported under comparisons 7 and 9. Similarly for Porcile 1991 we have reported the data under comparison 12 and 13.

Primary outcomes

Participant-reported improvement of hirsutism

Change in health-related quality of life (HRQOL)

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event

Only Bhattacharya 2012 reported data for this outcome. In the group treated with EE+ CPA 2/50 participants reported an adverse event and in the EE + desogestrel group 5/50 experienced adverse events (RR 0.41, 95% CI 0.08 to 2.05; P value = 0.28).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

We were able to pool the data for mean change from baseline in the Ferriman-Gallwey score from three of the studies (Bhattacharya 2012; Mastorakos 2002; Mastorakos 2006). Both treatment arms showed clinically meaningful reductions in the Ferriman-Gallwey score but the mean difference between the EE + CPA group and EE + desogestrel group was -1.84, which was not statistically significant (95% CI -3.86 to 0.18; P value = 0.07 and I^2 = 45%) (see Analysis 4.1).

The Lorenzo score was used in Porcile 1991 and reached similar conclusions (MD 0.20, 95% CI -6.30 to 6.70; P value = 0.95; see Analysis 4.2).

Change in serum androgen levels

The details for the changes in serum androgen levels are listed in Analysis 4.3. In Bhattacharya 2012 there were statistically significant differences between the two study arms for SHBG and the Free Androgen Index. The more substantial increase in SHBG reported in this study in the EE + CPA group closely correlates with the increased reduction in free androgen excess in this group. For this individual study this was also reflected in a statistically significant reduction of mean change in Ferriman-Gallwey score, an effect that was lost when we pooled the data (see Analysis 4.1).

Change in BMI

Two studies addressed this outcome (Bhattacharya 2012; Mastorakos 2006). There were small changes compared to baseline in the BMI, and no statistically significant changes between the two groups in both studies. In Bhattacharya 2012 the reductions in BMI were 0.59 kg/m² (4.76) for the EE + CPA group and 0.45 kg/m² (6.75) for the EE + desogestrel group (MD -0.14 kg/m², 95% CI -2.44 to 2.16; P value = 0.90). In Mastorakos 2006 the reductions in BMI were 0.6 kg/m² (4.41) and 0.7 kg/m² (4.61) respectively, with a MD of 0.10 kg/m² (95% CI -2.85 to 3.05; P value = 0.95).

Improvement of other clinical signs of hyperandrogenism

Only Bhattacharya 2012 reported data for this outcome. The mean changes in acne score showed a reduction of 1.52 (1.25) in the EE + CPA group and 1.41 (1.32) in the EE + desogestrel group. There was no statistically significant difference between the two treatment groups (MD -0.11, 95% CI -0.61 to 0.39; P value = 0.67).

(9) Ethinyl estradiol + drospirenone versus ethinyl estradiol 30 μg + desogestrel 0.15 mg for 12 months

Both Bhattacharya 2012 and Kriplani 2010 provided usable data for this comparison. One of these studies, Bhattacharya 2012, had three treatment arms (the other two comparisons are listed in comparison 7 and 8). In Kriplani 2010 only nine of the 60 participants were hirsute, but separate data were provided for the Ferriman-Gallwey-score assessments but not for the other analyses.

Primary outcomes

Participant-reported improvement of hirsutism

Change in health-related quality of life (HRQOL)

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event

There was no statistically significant difference in the number of adverse events reported between the two oral contraceptive pills (OCPs) in both of the studies. In Bhattacharya 2012 2/57 of the participants in the EE + drospirenone group reported an adverse event versus 5/58 in the EE + desogestrel group (RR 0.41, 95% CI 0.08 to 2.01; P value = 0.27). In Kriplani 2010 adverse events

were reported by 12/30 in the EE + drospirenone group compared to 19/30 in the EE + desogestrel group (RR 0.63, 95% CI 0.38 to 1.06; P value = 0.08). Both treatment groups reported similar side effects, i.e. nausea, abdominal pain, breakthrough bleeding, and bloating.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

There were slight reductions in the mean Ferriman-Gallwey score for the two interventions in Bhattacharya 2012 of 2.12 (6.58) for the EE + drospirenone group, and 1.69 (5.69) in the EE + desogestrel group (MD -0.43, 95% CI -2.85 to 1.99; P value = 0.73). In Kriplani 2010 the respective changes in mean Ferriman-Gallwey score were 4.6 (2.79) based on 5/30 of the participants who were hirsute in the EE + drospirenone group versus 0 (0.28) in 4/30 of those in the EE + desogestrel group, with a MD of -4.60 (95% CI -7.06 to -2.14; P value = 0.0002), a difference that is unlikely to be clinically important.

Change in serum androgen levels

There were minimal changes from baseline in the serum androgen levels in both groups and with minimal differences between the groups (see Analysis 5.1). The difference in mean changes in SHBG level in Bhattacharya 2012 and the testosterone level in Kriplani 2010 were statistically significant, but not clinically important with respect to any difference in the improvement of hirsutism.

Change in BMI

The changes from baseline in both treatment arms in both studies were small and there were no statistically significant differences between the groups (Bhattacharya 2012; Kriplani 2010). The BMI changes in Bhattacharya 2012 showed an increase of 0.11 kg/m² (5.54) for the EE + drospirenone group and a decrease of 0.45 kg/m² (6.75) for the EE + desogestrel group (MD 0.56 kg/m², 95% CI -1.88 to 3.00; P value = 0.65). In Kriplani 2010 the BMI changes were a decrease of 0.6 kg/m² (3.38) for the EE + drospirenone group and increase of 1.4 kg/m² (2.28) for the EE + desogestrel group (MD -2.00 kg/m², 95% CI -3.48 to -0.52; P value = 0.008), which is a statistically significant difference and correlates with the greater reduction in Ferriman-Gallwey score for the EE + drospirenone group.

Improvement of other clinical signs of hyperandrogenism

The instrument used to assess this outcome differed between the two studies and therefore it was not possible to pool the data. In Bhattacharya 2012 the mean change from baseline in acne score was a reduction of 1.42 (1.27) in the EE + drospirenone group and for the EE + desogestrel group 1.41 (1.32). The mean difference between the two OCPs was -0.01 (95% CI -0.52 to 0.50; P value = 0.97). Comparable data were reported in Kriplani 2010: 5/10 participants with acne in the EE + drospirenone group responded versus 3/10 in the EE + desogestrel group (RR 1.67, 95% CI 0.54 to 5.17; P value = 0.38).

(10) Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus placebo for 12 months

One study with a small sample size, assessed at high risk of bias, provided some usable data for this comparison (Saeed 1993).

Primary outcomes

Participant-reported improvement of hirsutism

Seven out of the 10 participants in the EE + CPA group considered themselves cured compared to 0/10 in the placebo group, which was a statistically significant and clinically important difference (RR 15.00, 95% CI 0.97 to 231.84; P value = 0.05, NNTB = 2, 95% CI 2 to 3). A further two participants in each treatment group considered themselves slightly improved (RR 1.00, 95% CI 0.17 to 5.77; P value = 1.00).

Change in health-related quality of life (HRQOL)

Proportion of participants who reported an adverse event

Neither of the above outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

This outcome was not reported (see 'Risk of bias' assessment under 'Characteristics of included studies' for this study (Saeed 1993)).

Change in serum androgen levels

This outcome was poorly reported for the active treatment group and not reported for the placebo group (see 'Risk of bias' assessment under 'Characteristics of included studies').

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(11) Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus other OCP (unknown) for three months

One study of short duration and assessed at high risk of bias reported very limited usable data for this comparison (Taheripanah 2010). We were unable to contact the investigators and it was unclear from the report which OCP had been evaluated.

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

At the end of three months there was no statistically significant difference in mean reduction of the Ferriman-Gallwey score between the two groups. The mean reduction in the EE + CPA group was 2.27 (7.97) compared to 2.13 (8.44) for the other OCP group (MD -0.14, 95% CI -4.29 to 4.01; P value = 0.95).

Change in serum androgen levels

Two serum androgens (free testosterone and dehydroepiandrosterone sulphate (DHEAS)) were measured and there were no statistically significant reductions in means of these values compared to baseline either within or between the two groups (see Analysis 6.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(12) Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 50 μg + desogestrel 0.15 mg for two years

A single study with three treatment arms reported data for this comparison (Porcile 1991, see also comparison 8 and 13).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean reductions in the Lorenzo score for the EE + CPA group were 7 (9.79) and for the EE50 + desogestrel group 5.7 (1.69), with a MD of -1.30 (95% CI -7.87 to 5.27; P value = 0.70).

Change in serum androgen levels

Minimal data were provided (see Analysis 7.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(13) Ethinyl estradiol 30 μg+ desogestrel 0.15 mg versus ethinyl estradiol 50 μg + desogestrel 0.15 mg for two years

One study with three treatment arms addressed this comparison (Porcile 1991, see also comparison 8 and 12).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The reductions in Lorenzo score seen within both groups were 7.20 (1.84) in the EE30 + desogestrel group and 5.7 (1.69) for the EE50 + desogestrel group, but there was no statistically significant difference in the mean values between the two treatment arms (MD -1.50, 95% CI -3.37 to 0.37; P value = 0.12).

Change in serum androgen levels

Minimal data were provided (see Analysis 8.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(14) Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 μg and levonorgestrel 0.15 mg for nine months

This comparison was evaluated in one trial (Breitkopf 2003).

Primary outcomes

Participant-reported improvement of hirsutism

Based on a non-specific questionnaire, 6/11 participants in the EE + desogestrel group reported a decrease in hair growth compared to 5/10 in the EE + levonorgestrel group (RR 1.09, 95% CI 0.48 to 2.48; P value = 0.84).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

Three adverse events were reported in the EE + desogestrel group and two in the EE + levonorgestrel group (RR 1.57, 95% CI 0.29 to 8.53; P value = 0.60).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean reduction in Ferriman-Gallwey score was 6.40 (4.79) in the EE + desogestrel group and 3.1 (3.81) in the EE + levonorgestrel group. The mean difference between the two treatment arms was -3.30 (95% CI -6.99 to 0.39; P value = 0.08). This difference is not statistically significant.

Change in serum androgen levels

The data for the changes in serum androgen levels are reported in Analysis 9.1, and in most instances the mean differences were statistically significant in favour of EE + desogestrel.

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(15) Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 30 μg + chlormadinone acetate 2 mg for six months

One study at unclear risk of bias with 55 participants provided usable data for this comparison (Lello 2008).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean reduction in the Ferriman-Gallwey score in the OCP including drospirenone group was 6.78 (1.25), as compared to a smaller reduction of 4.85 (1.13) in the OCP including chlormadinone group and, although the mean difference was statistically significant (-1.93, 95% CI -2.56 to -1.30; P value < 0.001), it was not clinically important.

Change in serum androgen levels

Reductions in androstenedione and testosterone levels favoured EE + drospirenone, however, as with the mean difference in Ferriman-Gallwey score, the differences were not clinically important or associated with any important change in the improvement of hirsutism (see Analysis 10.1).

Change in BMI

There was a slight increase in BMI in both groups; 0.58 kg/m² (1.64) in the EE + drospirenone group and 0.26 kg/m² (1.67) in the EE + chlormadinone group, with a MD of 0.32 kg/m² (95% CI -0.56 to 1.20; P value = 0.48), but the difference was not statistically significant.

Improvement of other clinical signs of hyperandrogenism

Acne was scored on a four-point Likert scale (0 = no acne and 3 = severe acne). The reduction in score in the EE + drospirenone group was 1.97 (0.27) and was slightly less at 1.75 (0.28) for the comparator group (MD -0.22, 95% CI -0.37 to 0.07; P value = 0.003).

(16) Ethinyl estradiol 30 μg + desogestrel 0.15 mg every month versus ethinyl estradiol 30 μg + desogestrel 0.15 mg every other month for two years

Only one three-armed study with a small sample size compared these interventions and provided relevant outcomes data (Porcile 1991B) (see also comparison 17 and 18).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The participants in the EE + desogestrel every month group showed a small and clinically unimportant mean reduction in the Lorenzo score of 1.40 (1.90) versus no reduction 0 (1.79) in the bi-monthly comparator group (MD -1.40, 95% CI -3.30 to 0.50; P value = 0.15).

Change in serum androgen levels

There were minimal changes in serum androgen levels for both treatment arms, which were not clinically important with respect to a difference in the improvement of hirsutism (see Analysis 11.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(17) Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus placebo for 24 weeks to two years

This comparison was evaluated in Hoeger 2008 (study 1) for a period of 24 weeks (see also comparison 2, 32, and 103, 105, and 112) and for two years in Porcile 1991B (see also comparison 16 and 18).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

In Hoeger 2008 (study 1) the mean Ferriman-Gallwey score showed a reduction of 1.20 (2.21) in the OCP group compared to a reduction of 0.90 (3.25) in the placebo group (MD -0.30, 95% CI -2.74 to 2.14; P value = 0.81). The mean reduction in Lorenzo score in Porcile 1991B was 1.40 (1.90) in the EE + desogestrel group, whereas the placebo group showed an increase of 3.20 (1.61). The MD was -4.60, 95% CI -6.48 to -2.72; P value < 0.001), which is a statistically significant difference but unlikely to be clinically important.

Change in serum androgen levels

There were no clinically important changes with respect to a difference in the improvement of hirsutism in serum androgen levels in either group (see Analysis 12.1).

Change in BMI

This was only assessed in Hoeger 2008 (study 1). There was a reduction of 1.40 (3.33) in the OCP group and a smaller reduction of 0.60 (4.57) in the placebo group (MD -0.80, 95% CI -4.30 to 2.70; P value = 0.65).

Improvement of other clinical signs of hyperandrogenism

This outcome was not assessed in Porcile 1991B and in Hoeger 2008 (study 1) data were inadequately reported and of limited value.

(18) Ethinyl estradiol 30 μg + desogestrel 0.15 mg every other month versus placebo for two years

A single study reported few usable data for this comparison (Porcile 1991B) (see also comparison 16 and 17).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

There was no change in the mean Lorenzo score in the active treatment group but there was a small increase of 3.20 (1.61) in the placebo group, with a MD of -3.20 (95% CI -5.21 to -1.19; P value = 0.002).

Change in serum androgen levels

The changes in serum androgen levels within each group as well as between the two treatment groups were not statistically significant (see Analysis 13.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(19) Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 μg + gestodene 75 μg for six months

A single study with 34 participants reported data for this comparison (Sobbrio 1990).

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

There were minor differences in reduction of the mean Ferriman-Gallwey score between the two OCPs of 5.20 (4.59) for the EE + desogestrel group and 4.30 (5.51) for the EE + gestodene group, MD -0.90 (95% CI -4.31 to 2.51; P value = 0.60).

Change in serum androgen levels

No important nor statistically significant differences were found in serum androgen levels between the two groups (see Analysis 14.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(20) Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 20 μg + drospirenone 3 mg for six months

Only one study provided limited data for this comparison (Oner 2011).

Primary outcomes

Participant-reported improvement of hirsutism

Change in health-related quality of life (HRQOL)

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event

The authors provided no data but reported that there were no serious side effects in either group.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

Both OCPs showed clinically important reductions in Ferriman-Gallwey scores of 8.60 (3.53) in the 30 μg EE OCP group and 9.60 (3.06) for the 20 μg EE OCP group. However, there were no statistically significant differences in these assessments of efficacy between the two OCPs (MD 1.00, 95% CI -0.89 to 2.89; P value = 0.30).

Change in serum androgen levels

There were no statistically significant differences in serum androgen levels for both treatment groups (see Analysis 15.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

Antiandrogens

(21) Flutamide 250 mg twice daily versus placebo for six to 12 months

This comparison was evaluated in two studies, both of which had four arms (Gambineri 2006; Moghetti 2000). Study duration in Gambineri 2006 was one year and the other possible comparisons of this study are addressed under comparisons 32, 46 to 48, and 110. The duration of intervention in Moghetti 2000 was six months (see also comparisons 22, 23, 25, 109, and 111).
In Gambineri 2006 in the first month the women were placed on a standardised hypocaloric diet (1200 to 1420 kcal/daily) and randomised subsequently, whilst continuing dietary treatment.

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was not assessed in Gambineri 2006. In Moghetti 2000 8/10 participants in the flutamide group considered themselves to have a good to excellent improvement compared to 0/10 in the placebo group (RR 17.00, 95% CI 1.11 to 259.87; P value = 0.04, NNTB = 2, 95% CI 1 to 2), which suggests a large and clinically important difference, albeit based on a study with a very small sample size.

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

In Gambineri 2006 four out of the 20 participants in the flutamide group reported adverse events (gastrointestinal discomfort) versus none out of the 20 in the placebo group (RR 9.00, 95% CI 0.52 to 156.91; P value = 0.13). In Moghetti 2000 1/10 of the participants in the flutamide group reported sleepiness and hyporexia and 1/10 in the placebo group reported mild headache and nausea (RR 1.00, 95% CI 0.07 to 13.87; P value = 1.00).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

In Gambineri 2006 there was a clinically important reduction in the Ferriman-Gallwey score in the flutamide group of 8.90 (5.53) and a small reduction in the placebo group of 1.30 (2.89) demonstrating a statistically significant and clinically important difference (MD -7.60, 95% CI -10.53 to -4.67; P value < 0.001).
In Moghetti 2000 there was a smaller mean reduction of 6.40 (3.42) in the flutamide group compared with an increase of 0.80 (3.32) in the placebo group, with a MD of -7.20 (95% CI -10.15 to -4.25; P value < 0.001).
In Moghetti 2000 the mean hair shaft diameter showed a reduction of 33 (24.70) µm in the flutamide group and an increase of 3 (21.64) µm in the placebo group (MD -36.00 µm, 95% CI -56.35 to -15.65; P value = 0.0005).

Change in serum androgen levels

In Gambineri 2006 the mean differences in androstenedione and DHEAS between the two treatment groups were statistically significant, but not for testosterone and SHBG, and in Moghetti 2000 only for androstenedione (see Analysis 16.1).
Change in BMI
This was only assessed in Gambineri 2006. There was a substantial reduction of 4.00 kg/m² (2.41) in the flutamide group and a smaller reduction in the placebo group of 2.00 kg/m² (3.16) (MD -2.00 kg/m², 95% CI -3.83 to -0.17; P value = 0.03). Reduction in weight loss was most probably due to the calorie restriction diet.

Improvement of other clinical signs of hyperandrogenism

The mean number of menses in the previous six months at the end of the study (Gambineri 2006) increased by 1.30 (1.08) in the flutamide group compared to 0.50 (0.76) in the placebo group (MD 0.80, 95% CI 0.18 to 1.42; P value = 0.01). This outcome was not assessed in Moghetti 2000.

(22) Flutamide 250 mg once to twice a day versus spironolactone 100 mg once a day for six to nine months

Two small sample size studies, which examined 20 participants, reported data for this comparison (Erenus 1994; Moghetti 2000). One of these, Moghetti 2000, was a four-armed study (see comparison 21, 23, 25, 109, and 111). The dosage of flutamide used in Erenus 1994 was 250 mg twice a day for nine months, and in Moghetti 2000 250 mg once a day for six months.

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was only assessed in Moghetti 2000. In the flutamide group 8/10 participants considered the improvement in hirsutism as good to excellent compared to 4/10 participants in the spironolactone group, with a RR of 2.00 (95% CI 0.88 to 4.54; P value = 0.10).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

In Erenus 1994 in the flutamide group 2/10 participants reported a side effect (both dry skin) compared to 5/10 participants in the spirolactone group (all five had irregular bleeding) (RR 0.40, 95% CI 0.10 to 1.60; P value = 0.20). In Moghetti 2000 1/10 in the flutamide group reported sleepiness and hyporexia compared to 5/10 in the spironolactone group who reported metrorrhagia (RR 0.20, 95% CI 0.03 to 1.42; P value = 0.11).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

In Erenus 1994 both treatment options demonstrated a clinically important reduction in Ferriman-Gallwey score of 9.80 (3.71) in the flutamide group and 7.90 (3.37) in the spironolactone group. However, there was no statistically significant difference between the two treatment arms (MD -1.90, 95% CI -5.01 to 1.21; P value = 0.23). These reductions were somewhat smaller in Moghetti 2000, which may be explained by the fact that the study duration was three months shorter and the dosage of flutamide was half of the dosage used in Erenus 1994. In Moghetti 2000 the mean Ferriman-Gallwey score reduced by 6.40 (3.42) in the flutamide group and in the spironolactone group by 6.89 (2.09), with a MD of 0.49 (95% CI -1.99 to 2.97; P value = 0.70). In addition, the mean hair shaft diameter decreased by 33 (24.70) µm in the flutamide group and by 20 (23.33) µm in the spironolactone group (MD -13.00 µm, 95% CI -34.06 to 8.06; P value = 0.23).

Change in serum androgen levels

There were no clinically important differences in changes of the androgen levels with respect to a difference in the improvement of hirsutism as there were no statistically significant differences in the mean Ferriman-Gallwey score between the groups for both studies (see Analysis 17.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(23) Spironolactone 100 mg per day versus placebo for six months

One four-armed study with small sample size examined these interventions (Moghetti 2000) (see also comparison 21, 22, 25, 109, and 111).

Primary outcomes

Participant-reported improvement of hirsutism

In the spironolactone group 4/10 considered themselves to have a good to excellent improvement compared to 0/10 in the placebo group (RR 9.00, 95% CI 0.55 to 147.95; P value = 0.12).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

In the spironolactone group 5/10 participant reported metrorrhagia and 1/10 in the placebo group experienced mild headache and nausea (RR 5.00, 95% CI 0.70 to 35.50; P value = 0.11).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean Ferriman-Gallwey score reduced by 6.89 (2.09) in the spironolactone group and showed a slight increase in the placebo group of 0.80 (3.32), with a MD of -7.69 (95% CI -10.12 to -5.26; P value < 0.001). This difference is statistically significant and clinically important.

Change in serum androgen levels

There were no statistically significant differences in changes in androgen levels between the spironolactone group and the placebo group, except for DHEAS in favour of placebo (see Analysis 18.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(24) Ketoconazole 400 mg per day versus ketoconazole 800 mg per day for 10 days

One study with a small sample size reported limited data on the effects of ketoconazole (Cedeno 1990), which is seldom used in view of its hepatic toxicity. Our only outcome addressed in this study was the change in serum androgen levels, which showed no statistically significant differences between the two groups (see Analysis 19.1).

5α reductase inhibitors

(25) Finasteride 5 mg to 7.5 mg once a day versus placebo for six to nine months

Three studies with a small sample size compared these interventions (Ciotta 1995; Lakryc 2003; Moghetti 2000). One of these, Moghetti 2000, was a four-armed study (see also comparison 21 to 23, 109, and 111).

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was assessed in Lakryc 2003 on a three-point Likert scale (amelioration, indifference, worse). In the finasteride group 11/16 participants considered themselves improved, compared to 6/18 in the placebo group (RR 2.06, 95% CI 0.99 to 4.29; P value = 0.05). In Moghetti 2000 it was assessed on a four-point Likert scale and 5/10 participants in the finasteride group considered themselves to have a good to excellent improvement compared to 0/10 in the placebo group (RR 11.00, 95% CI 0.69 to 175.86; P value = 0.09).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

There were no statistically significant differences between the groups in the number of adverse events. In Ciotta 1995 6/9 participants in the finasteride group reported an adverse event compared to 7/9 in the placebo group. These consisted of headache, depression, and dizziness, which were reported in both groups. In Lakryc 2003 3/16 participants in the finasteride group experienced side effects versus 1/18 in the placebo group. In Moghetti 2000 1/10 participants in the finasteride group reported 'being swollen' compared to 1/10 participants in the placebo group that complained of mild headache and nausea. Pooled data from the three trials showed RR 1.13 (95% CI 0.48 to 2.67; P value = 0.78 and I^2 = 18%) (see Analysis 20.1). The denominator of Moghetti 2000 is partitioned in the finasteride group as these data were also pooled in comparison 121.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

Pooled data from the three studies showed that the MD in mean Ferriman-Gallwey score between the finasteride group and the placebo group was -5.73 (95% CI -6.87 to -4.58; P value < 0.001 and I^2 = 0%), which is a statistically significant difference, however the difference is unlikely to be clinically important (see Analysis 20.2).

Change in serum androgen levels

The results of the changes in serum androgen levels are reported in Analysis 20.3. As would be expected finasteride reduces the conversion of testosterone into dihydrotestosterone, and thus there was a statistically significant mean difference in reduction of the dihydrotestosterone levels in the finasteride groups. Pooling of the data for the androgens was only possible for androstenedione and DHEAS (for free testosterone $I^2 > 60\%$), but there were no statistically significant changes between the two treatment arms for these two androgens (data not reported).

Change in BMI

This outcome, which was only assessed in one of the studies (Lakryc 2003), illustrated minimal changes in both treatment groups (-0.50 kg/m² (1.53) in the finasteride group and an increase of 0.80 kg/m² (2.50) in the placebo group), with a MD of -1.30 kg/m² (95% CI -2.96 to 0.36; P value = 0.12).

Improvement of other clinical signs of hyperandrogenism

This outcome was not assessed.

(26) Finasteride 2.5 mg once a day versus finasteride 5 mg once a day for six to 12 months

The effects of these interventions were evaluated in two studies at high risk of bias (Al-Khawajah 1998; Bayram 2002). One of these, Al-Khawajah 1998, was a three-armed study (see also comparison 27 and 28).

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was assessed in only one of the studies, Al-Khawajah 1998, in which the investigators used a five-point Likert scale (-1 = worse, 3 = much improved). After six months the group using the 2.5 mg formulation of finasteride had a mean score of 1.6 (0.5) and in the 5 mg group 1.7 (0.4), with both groups showing slight to moderate improvement (MD -0.10, 95% CI -0.42 to -0.22; P value = 0.55).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

The reporting of adverse events in Al-Khawajah 1998 was inadequate: only that there were two adverse events, and it remains unclear in which group these occurred. In Bayram 2002 there was a statistically significant increase in the number of adverse events with the higher dosage (5 mg) of finasteride. In the 2.5 mg dose group 5/29 participants reported an adverse event compared to 12/27 in the 5 mg group (RR 0.39, 95% CI 0.16 to 0.96; P value = 0.04; number needed to find one additional harmful outcome (NNTH) = 4, 95% CI 2 to 26). Adverse events included well-known side effects such as dry skin, headache, reduction in libido, and gastrointestinal complaints.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

There was a clinically important reduction in mean Ferriman-Gallwey score for both dosages. The reductions in Bayram 2002 were slightly more than in Al-Khawajah 1998, which was probably attributable to the six-month longer treatment time in the former study. In Al-Khawajah 1998 the reductions were 7.4 (0.5) in the 2.5 mg finasteride group and 7.2 (0.4) in the 5 mg group (MD -0.20, 95% CI -0.52 to 0.12; P value = 0.23). The reductions in Bayram 2002 were 9.8 (2.81) and 8.4 (3.23), which are clinically important changes, but the MD was not statistically significant (-1.40, 95% CI -2.99 to 0.19; P value = 0.08).

Reduction in hair shaft diameter was also assessed in Al-Khawajah 1998. The reduction in the 2.5 mg group was 24.8% (standard deviation (SD) 3.9) and in the 5 mg group 24.2% (4.2), with a MD of -0.60% between the groups (95% CI -3.50 to 2.30; P value = 0.69).

Change in serum androgen levels

The changes in serum androgens were not statistically significant (except for androstenedione in Bayram 2002) and are summarised in Analysis 21.1.

Change in BMI

This was only assessed in Bayram 2002 in which there was a reduction of 0.90 kg/m² (3.26) in the 2.5 mg group and 3.1 kg/m² (2.70) in the 5 mg group (MD 2.20 kg/m², 95% CI 0.64 to 3.76; P value = 0.006). The reduction in the 5 mg group was substantial and the difference between the groups is statistically significant, but this did not correlate with a statistically significant difference in the Ferriman-Gallwey score.

Improvement of other clinical signs of hyperandrogenism

This was not assessed in Al-Khawajah 1998, and the investigators in Bayram 2002 only reported that the menstrual cycles were not affected by the treatments.

(27) Finasteride 2.5 mg once a day versus finasteride 7.5 mg once a day for six months

A single three-armed study in 45 participants reported data for this comparison (Al-Khawajah 1998, see also comparison 26 and 28).

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was assessed with a five-point Likert scale (see comparison 26). The scores after six months were 1.6 (0.5) for the 2.5 mg group, and 2.3 (0.2) for the 7.5 mg group, with a MD of -0.70 (95% CI -0.97 to -0.43; P value < 0.001), which is a statistically significant difference in favour of the higher dosage. However, the clinical importance of this difference is difficult to interpret.

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

It was unclear from the report if there were one, two, or no adverse events in the 2.5 mg group, as compared to four which were reported in the 7.5 mg group and consisted of menstrual abnormalities and breast tenderness.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

Both treatment arms showed clinically important reductions in the mean Ferriman-Gallwey score of 7.4 (0.5) for the 2.5 mg group and 9.9 (0.2) for the 7.5 mg group. Although the mean difference of 2.50 (95% CI 2.23 to 2.77; P value < 0.001) is statistically significant, it is not clinically important. There was also a statistically significant difference in reduction in hair shaft diameter in favour of the higher dosage. There was a reduction of 24.8% (3.9) in the 2.5 mg group and 35.8% (2.9) in the 7.5 mg group (MD 11.00%, 95% CI 8.54 to 13.46; P value < 0.001). Although the 5 mg dose is the most frequently prescribed, the results in comparisons 25 to 27 suggest that a dosage of 2.5 mg would be sufficient enough to achieve a beneficial effect.

Change in serum androgen levels

There were no statistically significant differences between the two treatment arms for the serum androgens (see Analysis 22.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(28) Finasteride 5 mg once a day versus finasteride 7.5 mg once a day for six months

This comparison was also addressed by Al-Khawajah 1998 (see comparison 26 and 27).

Primary outcomes

Participant-reported improvement of hirsutism

This outcome was assessed on a five-point Likert scale (see also comparison 26). The end of study scores at six months were 1.7 (0.4) for the 5 mg group and 2.3 (0.2) for the 7.5 group (MD -0.60, 95% CI -0.83 to -0.37; P value < 0.001), which is a statistically significant difference between the groups in favour of the higher dosage. However, the clinical importance of this difference is difficult to interpret.

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

There were four adverse events in the 7.5 mg group and it was unclear how many there were in the 5 mg group (0 to 2).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean reduction in the Ferriman-Gallwey score was 7.2 (0.4) in the 5 mg group compared to 9.9 (0.2) in the 7.5 mg group, which were both clinically important. There was a statistically significant MD between the two groups of 2.7 (95% CI 2.47 to 2.93; P value < 0.001), but this was not considered clinically important.

Change in serum androgen levels

There were no statistically significant differences between the two treatment arms for serum androgens (see Analysis 23.1).

Change in BMI

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(29) Finasteride 2.5 mg once a day versus finasteride 2.5 mg every three days for 10 months

Only one study with a small sample size evaluated this comparison (Tartagni 2004).

Primary outcomes

Participant-reported improvement of hirsutism

The participants rated their assessments on a four-point Likert scale (worsening to good-excellent). Both intervention groups reported similar beneficial results; in the 2.5 mg daily group 16/19 considered the result good-excellent compared to 15/19 in the 2.5 mg every three days group (RR 1.07, 95% CI 0.79 to 1.44; P value = 0.68).

Change in health-related quality of life (HRQOL)

This outcome was not assessed.

Proportion of participants who reported an adverse event

One participant in the 2.5 mg daily group reported gastrointestinal discomfort (RR 3.00, 95% CI 0.13 to 69.31; P value = 0.49).

Secondary outcomes

Clinician's assessment of improvement of hirsutism

Both groups showed clinically important reductions in the modified Ferriman-Gallwey score; 9.85 (1.66) for the 2.5 mg daily group and 8.26 (2.28) for the 2.5 mg every three days group. The MD was -1.59 (95% CI -2.86 to -0.32; P value = 0.01), which was not considered a clinically important difference.

Change in serum androgen levels

There were no statistically significant differences in serum androgen levels between the two treatment arms, except for dihydrotestosterone, which was in favour of the 2.5 mg daily group (see Analysis 24.1).

Change in BMI

The reduction in mean BMI was small and comparable for both groups: 0.9 kg/m² (2.57) in the 2.5 mg daily group and 1.0 kg/m² (2.57) in the comparator group (MD 0.10 kg/m², 95% CI -1.53 to 1.73; P value = 0.90).

Improvement of other clinical signs of hyperandrogenism

There were no variations in the menstrual cycle in either group.

Insulin sensitisers

(30) Metformin 850 mg twice daily versus rosiglitazone 2 mg twice daily for 12 months

Although rosiglitazone is no longer used in Europe, it is still registered in the US and several other countries. This comparison was evaluated in Ahmad 2008.

Improvement of other clinical signs of hyperandrogenism

Neither of the above outcomes were assessed.

(133) Bromocriptine 2.5 mg three times a day versus placebo for 12 months

A small sample size study evaluated this comparison (Murdoch 1987).

Primary outcomes

Primary outcomes

Participant-reported improvement of hirsutism

Participant-reported improvement of hirsutism

This was assessed on a three-point Likert scale (worse, unchanged, improved). Four participants dropped out in the bromocriptine group, and of the remaining seven, two considered they had achieved an improvement although daily shaving was still necessary. None of the control group improved and there were 2/11 drop-outs.

Proportion of participants who reported an adverse event

Although it was not a prespecified outcome in the study, the investigators reported that 4/11 (36%) and that gastrointestinal disturbances such as nausea, diarrhoea, and abdominal bloating occurred more frequently in the metformin group. These are well-known side effects of metformin.

Proportion of participants who reported an adverse event

Neither of the above outcomes were assessed.

Secondary outcomes

Secondary outcomes

Clinician's assessment of improvement of hirsutism

There was a reduction in mean Ferriman Gallwey score of 4.31 (1.70) in the metformin group and 0.62 (1.30) in the rosiglitazone group (MD -3.69, 95% CI -4.67 to -2.91; P value < 0.001). The MD between the groups is statistically significant, albeit not clinically important.

Change in serum androgen levels

There were no statistically significant differences between the two treatment arms for serum androgens, except for androstenedione in favour of metformin (see Analysis 25.1).

Change in BMI

This outcome was not assessed.

Change in BMI

There were minimal changes in the mean BMI in both of the intervention groups. In the metformin group there was a reduction of 0.1 kg/m² (3.39) and in the rosiglitazone group a slight increase of 0.6 kg/m² (3.63), with a MD of -0.77 kg/m² (95% CI -2.53 to 0.99; P value = 0.39).

Improvement of other clinical signs of hyperandrogenism

At the end of the study 96% of the women in the metformin group had a regular cycle versus 90% in the rosiglitazone group, and 61% of the women in the metformin group were ovulating compared to 73% in the rosiglitazone group. There was a clear and increased improvement in these outcome data at each three-month time point.

(31) Troglitazone 150 mg versus troglitazone 300 mg versus troglitazone 600 mg versus placebo for 44 weeks

Troglitazone has been withdrawn from the market in the UK and the US due to concerns about possible hepatic toxicity. As this drug is not very likely to be prescribed for hirsutism, we have not subdivided the four arms into two-armed comparisons. Only one multi-centre study addressed these interventions (Azziz 2001), but the report was unclear how many participants were randomised to each arm; the investigators only reported how many participants completed the study in each arm (see Characteristics of included studies).

Primary outcomes

None of our primary outcomes were assessed. However, the investigators reported that 4% to 7% of the participants in each treatment arm withdrew due to side effects.

Secondary outcomes

Clinician's assessment of improvement of hirsutism

The mean change from baseline in the Ferriman-Gallwey score for each group was minimal and not clinically important: -0.51 (3.97) in the troglitazone 150 mg group, -0.80 (3.93) in the troglitazone 300 mg group, and -2.21 (3.86) in the troglitazone 600 mg group compared to -0.22 (4.00) in the placebo group.

Change in serum androgen levels

The changes in serum androgen levels are reported in Analysis 26.1. The reductions in free testosterone showed a dose-related effect.

Change in BMI

This outcome was not assessed.

Improvement of other clinical signs of hyperandrogenism

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Flutamide 250 mg b.i.d. compared to placebo for hirsutism

Patient or population: women with hirsutism
Intervention: flutamide 250 mg b.i.d.
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Flutamide 250 mg b.i.d.				
Participant-reported improvement of hirsutism 4-point Likert scale	**Study population**		**RR 17** (1.11 to 259.87)	20 (1 study)	⊕⊕◯◯ **low**[1]	Improvement as assessed on a Likert scale was good to excellent but based on a small sample size
	Low					
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants who reported an adverse event	See comment	See comment	Not estimable	60 (2 studies)	⊕◯◯◯ **very low**[1,2]	RR 9.00, 95% CI 0.52 to 156.91; P value = 0.13 (Gambineri 2006) and RR 1.00, 95% CI 0.07 to 13.87; P value = 1.00 (Moghetti 2000)
Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	See comment	See comment	Not estimable	60 (2 studies)	⊕◯◯◯ **very low**[1,2]	MD -7.60, 95% CI -10.53 to -4.67; P value < 0.001 (Gambineri 2006) and MD -7.20, 95% CI -10.15 to -4.25; P value <0.001 (Moghetti 2000)

						. Both studies demonstrated a statistically significant and clinically important difference in favour of the flutamide group
Change in serum androgen levels	See comment	See comment	Not estimable	60 (2 studies)	⊕⊕◯◯ **low**[1]	There were in both studies statistically significant differences in androstenedione levels in favour of the flutamide group
Change in BMI kg/m^2	The mean change in BMI in the control groups was **-2 kg/m^2**	The mean change in BMI in the intervention groups was **2.00 kg/m^2 lower** (3.83 kg/m^2 to 0.17 kg/m^2 lower)		40 (1 study)	⊕◯◯◯ **very low**[1,2]	All participants were on a calorie restriction diet
Improvement of other clinical signs of hyperandrogenism Mean number of menses in previous 6 months Scale from: 0 to 6	The mean improvement of other clinical signs of hyperandrogenism in the control groups was **0.50**	The mean improvement of other clinical signs of hyperandrogenism in the intervention groups was **0.8 higher** (0.18 to 1.42 higher)		40 (1 study)	⊕◯◯◯ **very low**[1,2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
b.i.d.: twice a day; **BMI:** body mass index; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded two levels due to very serious imprecision (very wide CI due to small sample size).
[2]Downgraded one level due to serious risk of selection bias (allocation concealment was assessed as 'high risk of bias' for Gambineri 2006).

Flutamide 250 mg once to b.i.d. compared to spironolactone 100 mg for hirsutism

Patient or population: women with hirsutism
Intervention: flutamide 250 mg once to b.i.d.
Comparison: spironolactone 100 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Spironolactone 100 mg	Flutamide 250 mg once to b.i.d.				
Participant-reported improvement of hirsutism 4-point Likert scale	**Study population**		**RR 2.00** (0.88 to 4.54)	20 (1 study[1])	⊕⊕◯◯ **low**[2]	
	400 per 1000	**800 per 1000** (352 to 1000)				
	Low					
	100 per 1000	**200 per 1000** (88 to 454)				
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study assessed this outcome
Proportion of participants who reported an adverse event	See comment	See comment	Not estimable	40 (2 studies[3])	⊕⊕◯◯ **low**[4,5]	RR 0.40, 95% CI 0.10 to 1.60; P value = 0.20 (Erenus 1994), RR 0.20, 95% CI 0.03 to 1.42; P value = 0.11 (Moghetti 2000)

Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	See comment	See comment	Not estimable	40 (2 studies[3])	⊕◯◯◯ **very low**[2,4]	MD -1.90, 95% CI -5.01 to 1.21; P value = 0.23 (Erenus 1994), 0.49, 95% CI -1.99 to 2.97; P value = 0.70 (Moghetti 2000)
Change in serum androgen levels	See comment	See comment	Not estimable	40 (2 studies[3])	⊕⊕⊕◯ **moderate**[2]	There were no clinically important differences in changes of the androgen levels with respect to a difference in the improvement of hirsutism
Change in BMI - not measured	See comment	See comment	Not estimable	-	See comment	No study assessed this outcome
Improvement of other clinical signs of hyperandrogenism - not measured	See comment	See comment	Not estimable	-	See comment	No study assessed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
b.i.d.: twice a day; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Moghetti 2000.
[2]Downgraded two levels due to very serious imprecision (wide CI due to low sample size, optimal information size not met by far).
[3]Erenus 1994, Moghetti 2000.
[4]Downgraded one level due to performance and detection bias (Erenus 1994 was an open-label study).
[5]Downgraded one level due to imprecision (wide CI, due to low sample size).

Spironolactone 100 mg compared to placebo for hirsutism

Patient or population: women with hirsutism
Intervention: spironolactone
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Spironolactone				
Participant-reported improvement of hirsutism 4-point Likert scale	**Study population**		**RR 9.00** (0.55 to 147.95)	20 (1 study)	⊕⊕◯◯ **low**[1]	No statistically significant difference between the 2 treatments, but based on a small sample size
	Low					
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	Outcome was not assessed
Proportion of participants who reported an adverse event	**Study population**		**RR 5.00** (0.7 to 35.5)	20 (1 study)	⊕⊕◯◯ **low**[1]	This difference is statistically significant, but based on a small sample size
	100 per 1000	**500 per 1000** (70 to 1000)				
	Low					
Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	The mean clinician's assessment of improvement of hirsutism in the control groups was **0.8**	The mean clinician's assessment of improvement of hirsutism in the intervention groups was **7.69 lower** (10.12 to 5.26 lower)		20 (1 study)	⊕⊕◯◯ **low**[1]	This difference is statistically significant and clinically important, but based on a small sample size

Change in serum androgen levels	See comment	See comment	Not estimable	20 (1 study)	⊕⊕◯◯ **low**[1]	There were no clinically important differences in changes in androgen levels between the spironolactone group and placebo group
Change in BMI - not measured	See comment	See comment	Not estimable	-	See comment	Outcome was not assessed
Improvement of other clinical signs of hyperandrogenism - not measured	See comment	See comment	Not estimable	-	See comment	Outcome was not assessed

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded two levels due to very serious imprecision (very wide CI due to small sample size).

Finasteride 5 mg to 7.5 mg compared to placebo for hirsutism

Patient or population: women with hirsutism
Intervention: finasteride 5 mg to 7.5 mg
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Finasteride 5 mg to 7.5 mg				
Participant-reported improvement of hirsutism 3-point (Lakryc 2003) and 4-point (Moghetti 2000) Likert scale	See comment	See comment	Not estimable	54 (2 studies)	⊕◯◯◯ **very low**[1,2]	RR 2.06, 95% CI 0.99 to 4.29; P value = 0.05 (Lakryc 2003) and RR 11.00, 95% CI 0.69 to 175.86; P value = 0.09 (Moghetti 2000)
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants who reported an adverse event	**Study population**		**RR 1.13** (0.48 to 2.67)	67 (3 studies)	⊕◯◯◯ **very low**[1,2]	
	243 per 1000	**275 per 1000** (117 to 649)				
	Moderate					
	200 per 1000	**226 per 1000** (96 to 534)				

Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	The mean clinician's assessment of improvement of hirsutism in the control groups was **0.8**	The mean clinician's assessment of improvement of hirsutism in the intervention groups was **5.73 lower** (6.87 to 4.58 lower)		62 (3 studies)	⊕○○○ **very low**[1,2]	MD is statistically significant, however the difference is unlikely to be clinically important
Change in serum androgen levels	See comment	See comment	Not estimable	52 (3 studies)	⊕⊕○○ **low**[2]	Finasteride reduces the conversion of testosterone into dihydrotestosterone; there was a statistically significant mean difference in reduction of DHT levels
Change in BMI kg/m^2	The mean change in BMI in the control groups was **0.8 kg/m^2**	The mean change in BMI in the intervention groups was **1.30 kg/m^2 lower** (2.96 kg/m^2 lower to 0.36 kg/m^2 higher)		24 (1 study)	⊕○○○ **very low**[2,3]	
Improvement of other clinical signs of hyperandrogenism - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **DHT:** dihydrotestosterone; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of bias (several domains have been judged as at unclear risk of bias (Ciotta 1995)).

[2]Downgraded one level due to very serious imprecision (very wide CI due to low sample size).
[3]Downgraded one level due to serious attrition bias (high drop-out rate of 29% and per-protocol analysis).

Metformin 500 mg to 2550 mg per day compared to placebo for hirsutism

Patient or population: women with hirsutism
Intervention: metformin 500 mg to 2550 mg per day
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Metformin 500-2550 mg per day				
Participant-reported improvement of hirsutism - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants who reported an adverse event	See comment	See comment	Not estimable	63 (2 studies)	⊕○○○ **very low**[1,2]	RR 5.00, 95% CI 0.26 to 98.00; P value = 0.29 (Gambineri 2006), RR 1.60, 95% CI 0.64 to 4.01; P value = 0.31 (Moghetti 2000B)
Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	The mean clinician's assessment of improvement of hirsutism ranged across control groups from **-1.3 to 9.6**	The mean clinician's assessment of improvement of hirsutism in the intervention groups was **0.05 higher** (1.02 lower to 1.12 higher)		264 (7 studies)	⊕⊕○○ **low**[3,4]	

Change in serum androgen levels	See comment	See comment	Not estimable	309 (8 studies)	⊕⊕⊕◯ **moderate**[3]	Most of the mean differences were not statistically significant nor clinically important
Change in BMI kg/m^2	The mean change in BMI ranged across control groups from **-2 to 0.4 kg/m^2**	The mean change in BMI in the intervention groups was **0.56 kg/m^{2}higher** (0.37 kg/m^2 lower to 1.5 kg/m^2 higher)		252 (5 studies)	⊕⊕⊕◯ **moderate**[4]	
Improvement of other clinical signs of hyperandrogenism - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious selection bias (allocation concealment was assessed as 'high risk of bias' for Gambineri 2006).
[2]Downgraded two levels due to very serious imprecision (very wide CI, due to low sample size).
[3]Downgraded one level due to serious risk of selection bias and attrition bias (allocation concealment was assessed as 'high risk of bias' for Gambineri 2006, high drop-out rate (39%), and per-protocol analysis for Hoeger 2004).
[4]Downgraded one level due to serious imprecision (wide CI, due to low sample size).

Finasteride 5 mg compared to spironolactone 100 mg for hirsutism

Patient or population: women with hirsutism
Intervention: finasteride 5 mg
Comparison: spironolactone 100 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Spironolactone 100 mg	Finasteride 5 mg				
Participant-reported improvement of hirsutism 4-point (Moghetti 2000) and 6-point (Wong 1995) Likert scale	See comment	See comment	Not estimable	34 (2 studies)	⊕⊕◯◯ **low**[1,2]	RR of 1.25, 95% CI 0.47 to 3.33; P value = 0.66 (Moghetti 2000) and RR 1.94, 95% CI 0.63 to 6.01; P value = 0.25 (Wong 1995)
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants who reported an adverse event	**Study population**		**RR 0.20** (0.03 to 1.41)	20 (1 study)	⊕⊕⊕◯ **moderate**[2]	
	500 per 1000	**100 per 1000** (15 to 705)				
	Low					
	100 per 1000	**20 per 1000** (3 to 141)				

Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	See comment	See comment	Not estimable	34 (2 studies)	⊕⊕◯◯ **low**[1,2]	MD 1.49, 95% CI -0.58 to 3.56; P value = 0.16 (Moghetti 2000) and MD 0.40, 95% CI -1.18 to 1.98; P value = 0.62 (Wong 1995)
Change in serum androgen levels	See comment	See comment	Not estimable	34 (2 studies)	⊕⊕◯◯ **low**[3]	No clinically important differences
Change in BMI - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Improvement of other clinical signs of hyperandrogenism - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of performance and detection bias (Wong 1995 no blinding reported).
[2]Downgraded one level due to serious imprecision (wide CI, due to low sample size).
[3]Downgraded two levels due to very serious imprecision (very wide CI, due to low sample size).

Flutamide 250 mg once to twice daily compared to metformin 1275 mg to 1700 mg per day for hirsutism

Patient or population: women with hirsutism
Intervention: flutamide 250 mg once to twice daily
Comparison: metformin 1275 mg to 1700 mg per day

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Metformin 1275 to 1700 mg per day	Flutamide 250 mg once to twice daily				
Participant-reported improvement of hirsutism - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No prespecified outcome, but in Esmaeilzadeh 2010 the investigators stated that the quality of life improved dramatically in both groups; however no additional data were provided
Proportion of participants who reported an adverse event	**Study population**		**RR 2** (0.41 to 9.71)	40 (1 study)	⊕◯◯◯ **very low**[1,2]	
	100 per 1000	**200 per 1000** (41 to 971)				
	Low					
	50 per 1000	**100 per 1000** (20 to 486)				

Clinician's assessment of improvement of hirsutism[3] Ferriman-Gallwey score Scale from: 0 to 36	See comment	See comment	Not estimable[3]	95 (3 studies)	⊕◯◯◯ **very low**[4,5,6]	MD -1.50, 95% CI -3.20 to 0.20; P value = 0.08 (Esmaeilzadeh 2010), MD -0.70, 95% CI -3.16 to 1.76; P value = 0.58 (Ibáñez 2002), MD -6.30, 95% CI -9.83 to -2.77; P value = 0.0005 (Gambineri 2006)
Change in serum androgen levels	See comment	See comment	Not estimable	95 (3 studies)	⊕⊕⊕◯ **moderate**[6]	No clinically important differences in changes in androgen levels between the 2 groups, except for androstenedione and DHEAS in Gambineri 2006 in favour of flutamide
Change in BMI[3] kg/m^2	See comment	See comment	Not estimable[3]	95 (3 studies)	⊕◯◯◯ **very low**[4,6,7]	MD 1.70 kg/m^2, 95% CI 0.49 to 2.91; P value = 0.006 (Esmaeilzadeh 2010), MD 2.00 kg/m^2, 95% CI -3.75 to -0.26; P value = 0.02 (Gambineri 2006), MD 0.50 kg/m^2, 95% CI -0.72 to 1.72; P value = 0.42 (Ibáñez 2002)
Improvement of other clinical signs of hyperandrogenism	See comment	See comment	Not estimable	55 (2 studies)	⊕⊕⊕◯ **moderate**[6]	MD in frequency of menstruations in the previous 6 months -0.70, 95% CI -1.40 to 0.00; P value = 0.05 (Gambineri 2006). More ovulatory cycles in metformin group (Ibáñez 2002)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CI:** confidence interval; **DHEAS :** dehydroepiandrosterone sulphate; MD: mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to serious risk of selection bias (allocation concealment was assessed as 'high risk of bias' for Gambineri 2006).
[2]Downgraded two levels due to very serious imprecision (very wide CI, due to low sample size).
[3]Downgraded one level due to substantial heterogeneity ($I^2 > 60\%$), pooling of data not feasible.
[4]Downgraded one level due to serious risk of selection bias, performance and detection bias (allocation concealment was assessed as 'high risk of bias' for Gambineri 2006, Ibáñez 2002 was not blinded).
[5]Downgraded one level due to heterogeneity (Gambineri 2006 demonstrated a larger effect in the flutamide group, probably due to longer treatment duration).
[6]Downgraded one level due to serious imprecision (wide CI, due to low sample size).
[7]Downgraded one level due to inconsistency (both arms had more weight loss in Esmaeilzadeh 2010 and Gambineri 2006 in which all participants were placed on a hypocaloric diet).

Finasteride 5 mg compared to flutamide 250 mg once to b.i.d. for hirsutism

Patient or population: women with hirsutism
Intervention: finasteride 5 mg
Comparison: flutamide 250 mg once to b.i.d.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Flutamide 250 mg once to b.i.d.	Finasteride 5 mg				
Participant-reported improvement of hirsutism 4-point Likert scale	**Study population**		**RR 0.63** (0.31 to 1.25)	20 (1 study)	⊕⊕◯◯ **low**[1]	Improvement as assessed on a Likert scale was good to excellent but based on a small sample size
	800 per 1000	**504 per 1000** (248 to 1000)				
	Low					
	100 per 1000	**63 per 1000** (31 to 125)				
Change in health-related quality of life (HRQOL) - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants who reported an adverse event	**Study population**		**RR 3.87** (0.57 to 26.24)	115 (3 studies)	⊕◯◯◯ **very low**[2,3]	
	17 per 1000	**64 per 1000** (9 to 437)				
	Low					
	10 per 1000	**39 per 1000** (6 to 262)				

Clinician's assessment of improvement of hirsutism Ferriman-Gallwey score Scale from: 0 to 36	See comment	See comment	Not estimable	226 (4 studies)	⊕◯◯◯ **very low**[1,4,5]	MD 3.62, 95% CI 3.04 to 4.20 (Falsetti 1999), MD 1.00, 95% CI -2.50 to 4.50 (Fruzzetti 1999), MD 1.00, 95% CI -1.66 to 3.66 (Moghetti 2000), and MD 5.20, 95% CI 3.46 to 6.94 (Müderris 2000)
Change in serum androgen levels	See comment	See comment	Not estimable	226 (4 studies)	⊕⊕⊕◯ **moderate**[1]	There were no clinically important differences in changes in androgen levels between the 2 treatment groups
Change in BMI - not measured	See comment	See comment	Not estimable	-	See comment	No study assessed this outcome
Improvement of other clinical signs of hyperandrogenism		The mean improvement of other clinical signs of hyperandrogenism in the intervention groups was **0 higher**		110 (1 study)	⊕⊕⊕⊕ **high**	No changes in menstrual cycles in either intervention group

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
b.i.d.: twice a day; **BMI:** body mass index; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded two levels due to very serious imprecision (wide CI, due to low sample size, optimal sample size is not met by far).
[2]Downgraded one level due to serious risk of performance and detection bias (Fruzzetti 1999 and Müderris 2000 were open studies).
[3]Downgraded two levels due to very serious imprecision (very wide CI, due to low sample size).

[4]Downgraded one level due to serious risk of performance and detection bias (Falsetti 1999, Fruzzetti 1999, and Müderris 2000 were open studies).
[5]Downgraded one level due to substantial and inexplicable heterogeneity (I^2 = 67%), caused by Müderris 2000.

DISCUSSION

Summary of main results

We included 157 studies with a total of 10,550 participants in this review. There was wide diversity in the types of interventions that were evaluated and some of them were either not specifically intended, or are not currently used, for treating hirsutism, e.g. insulin-sensitising agents, gonadotropin-releasing analogues, statins, clomiphene, or laparoscopic ovary diathermy or drilling. As some of these interventions had been evaluated in hirsute women and addressed several of our review outcomes, i.e. the Ferriman-Gallwey scores, we have included the relevant data from these studies in this systematic review. However, our 'Summary of findings' tables mainly cover those interventions that focus specifically on the treatment of hirsutism. We did not identify any randomised controlled trials addressing cosmetic measures such as waxing, shaving, or bleaching, nor any trials investigating the different methods of electrolysis, although these are frequently offered as treatment options. Laser and photoepilation therapy have already been assessed in another Cochrane review (Haedersdal 2006).

Two of our primary outcomes, 'participant-reported improvement of hirsutism' and 'change in health-related quality of life' were addressed but in only a few of the studies. Hirsutism in women occurs far more frequently than meets the eye and many women will do everything possible to rid themselves of the superfluous hairs. The psychosocial impact of hirsutism in women is well recognised and can affect an individual's self esteem and self image, leading to feelings of shame, psychological distress, depression, and to a reduction in overall quality of life. It was unfortunate that the importance of patient-reported outcomes (PROs) such as 'participant-reported improvement of hirsutism' and 'health-related quality of life' appears to have been underestimated and that these outcomes were overlooked by the investigators in the majority of the studies. Moreover, the studies that did address some of these outcomes did not, in most instances, use a validated measure or internationally recognised instrument.

Adverse events were evaluated and reported in less than half of the studies and as most of the interventions would require a lengthy treatment period the possibility of side effects occurring after protracted use should have been a consideration. Conversely it could be argued that, as most of the treatment options have been widely available for a considerable period of time, many if not all of these side effects are already well known. However, in most of the comparisons there were no statistically significant differences in the number of adverse events between either of the treatment arms. The side effects that were reported included mainly known adverse events such as gastrointestinal discomfort, breast tenderness, reduced libido, and dry skin with flutamide and finasteride; irregular bleeding with spironolactone; nausea, diarrhoea, and abdominal bloating with metformin; and hot flushes, decreased libido, vaginal dryness, breast tenderness, and headaches with the gonadotropin-releasing analogues.

The Ferriman-Gallwey score, which was one of our secondary outcomes, was used for the clinician's evaluation of hirsutism in most of the studies. Changes in serum androgen levels were also addressed in the majority of the studies. It was readily apparent that many of the laboratories used by study investigators applied their own units of measurement for the different androgens rather than following the International System of Units (Système Internationale or SI). In most of the comparisons these changes in androgen levels were not clinically important or not statistically significant, and therefore there would be limited benefit in converting all of these units to SI units. Change in body mass index (BMI) and improvement of other clinical signs of hyperandrogenism were evaluated in around one-third of the studies.

Pooling of data based on Ferriman-Gallwey score was possible in just three of the comparisons (OCP including cyproterone acetate versus OCP including desogestrel; finasteride versus placebo; metformin versus placebo), adverse events in two (finasteride versus placebo; finasteride versus flutamide), and BMI in only one of the comparisons (metformin versus placebo).

Although predominantly examined in single study comparisons, oral contraceptives (OCPs) reduced the Ferriman-Gallwey score, but the reduction was not shown to be consistently clinically important across the studies. It is acknowledged that OCPs gradually increase sex hormone-binding globulin (SHBG) levels and thereby decrease free testosterone levels and thus in studies with a duration of less than six months the SHBG increase might not have reached the plateau phase nor attained maximum effect. There was evidence, albeit rated as low quality, that OCP with ethinyl estradiol 35 µg + cyproterone acetate 2 mg and OCP with ethinyl estradiol 30 µg + desogestrel 0.15 mg are equally effective in reducing the Ferriman-Gallwey score in a clinically important manner (Summary of findings for the main comparison).

Evidence was available showing that one of the antiandrogens, flutamide 250 mg twice daily given for six to 12 months, was more effective in reducing the Ferriman-Gallwey score than placebo, a result that was both statistically significant and clinically important although we rated the evidence very low quality (see Summary of findings 2). In the combined treatment comparisons there were similar reductions in Ferriman-Gallwey score in the 'flutamide only' treatment arms. Spironolactone was also shown to be effective based on three comparisons (flutamide versus spironolactone, spironolactone versus placebo, and finasteride versus spironolactone in a dosage of 100 mg per day for six months) (see Summary of findings 3 and Summary of findings 4 for data on comparison 'flutamide versus spironolactone' and 'spironolactone versus placebo').

We rated the pooled data for the Ferriman-Gallwey score from three studies evaluating finasteride 5 mg to 7.5 mg per day, a 5α reductase inhibitor, as very low quality evidence and demonstrated that although there was a statistically significant difference in the

effectiveness of finasteride versus placebo, it was unlikely that this difference was clinically meaningful. These results were reinforced by the participant-reported assessments of improvement of hirsutism in two of the studies (see Summary of findings 5). Other comparisons including a 'finasteride monotherapy arm' showed limited to more substantial and clinically important decreases in Ferriman-Gallwey scores (see comparisons 26 to 28, 53, 107, 109, 111, and 117).

Metformin was the most frequently evaluated insulin sensitiser. Pooled data for the Ferriman-Gallwey score from seven studies demonstrated no statistically significant benefit of metformin over placebo but we rated the quality of evidence as low (see Summary of findings 6).

We were unable to pool data for the combined interventions of OCPs with cyproterone acetate 20 mg to 100 mg due to clinical and methodological heterogeneity between the studies. However, it was evident that the addition of cyproterone acetate to OCP did result in greater reductions in Ferriman-Gallwey scores than OCP alone. The results reported on the effectiveness of the gonadotropin-releasing analogues for hirsutism were inconsistent and varied from minimal improvements to clinically important improvements.

We had expected to find more evidence in support of the increased effectiveness of combination therapies of OCPs, i.e. combined with flutamide, finasteride, or spironolactone, but the results of this review failed to confirm this assumption. Two small studies, which compared finasteride 5 mg and spironolactone 100 mg for six months, did not show statistically significant differences in participant assessments and reduction of the Ferriman-Gallwey score (both rated as low quality evidence) (see Summary of findings 7).

Data on Ferriman-Gallwey scores, rated as very low quality evidence, from three studies comparing flutamide versus metformin could not be pooled due to substantial heterogeneity (I^2 = 62%). However, one study that compared flutamide 250 mg twice a day with metformin 850 mg twice a day for 12 months, and which reached a higher cumulative dosage than in the other two studies evaluating this comparison, showed a statistically significant difference in favour of flutamide (see Summary of findings 8). The data showing a reduction in Ferriman-Gallwey scores could not be pooled for the four studies comparing finasteride with flutamide due to substantial heterogeneity (I^2 = 67%) and the results were not consistent (see Summary of findings 9).

Several studies that examined the effects of hypocaloric diets reported reductions in BMI, but which did not appear to result in a greater reduction of the Ferriman-Gallwey score, although it was not possible to separate out the effect of reduction of BMI from the effect of the oral pharmacological treatments in terms of improvement of the hirsutism. It remains unclear if this could be attributed to a synergistic effect, i.e. an enhanced effect of the oral treatments with the additional increase of SHBG and the corresponding decrease of free testosterone induced by the weight loss. Only limited data were available for some of the other clinical signs of hyperandrogenism. Comparisons including OCPs showed a beneficial effect of the use of OCPs on acne, whilst insulin sensitisers seem to improve the menstrual pattern.

Overall completeness and applicability of evidence

A broad range of treatment options were covered by the studies included in this review, but we assessed the majority of these studies as at high risk of bias mainly due to inadequate blinding of participants, investigators, and outcome assessors. Pooling of study data was only possible for very few of the interventions as most of the 134 comparisons were examined in single studies. Consequently, no fair and reliable judgement could be made regarding which treatment option, or which combination of different therapies, is most effective. Considering the impact of hirsutism on a woman's mental, social, and physical well being there is a pressing need for studies that include patient-reported outcomes (PROs), which will help fill in some of the gaps about which treatments, according to the participants, are considered to be the most effective, tolerable, and acceptable.

Based on the available evidence the following interventions would appear to be at best both effective and safe: OCP with ethinyl estradiol 35 µg + cyproterone acetate 2 mg and OCP with ethinyl estradiol 30 µg + desogestrel 0.15 mg, as well as flutamide 250 mg twice daily, and spironolactone 100 mg per day for at least six to 12 months.

Quality of the evidence

The overall quality of the evidence across the different outcomes as summarised in the 'Summary of findings' tables was moderate to very low. The key reasons for downgrading the quality of the evidence for each outcome were: limitations in study design or execution (risk of bias) and imprecision mainly due to low sample size.

Limitations in study design and implementation

The 'Risk of bias' assessments as summarised in the 'Risk of bias in included studies' section of this review identified some of the limitations in study design in the included studies. In more than half of the studies the method used to generate the sequence was not adequately described and in almost three-quarters of them the method used to conceal the allocation was not reported. Furthermore, more than half of the studies had an open-label design, which represents a potential risk of performance and detection bias, and in almost half of the studies we judged the risk of attrition bias to be unclear to high as outcome data were incomplete. Achievement of the optimum effect will to a large extent depend on the duration of the treatment period as well as on the variable

rates of hair growth in different parts of the body. Although there is a widely supported recommendation that the duration of treatment should be not less than six months, some of the studies covered in this review evaluated interventions lasting just three to four months with a possibility that they may have shown somewhat limited beneficial treatment effect over this shorter time period (see Effects of interventions).

Indirectness of the evidence

The women included in the studies were fairly representative of the participants as prespecified in 'Types of participants'. Both placebo-controlled studies as well as active-controlled studies were included, and therefore for most treatment options it was possible to make a fair judgement on the comparative effectiveness of some of the individual treatments.

PROs (patient-reported outcomes) are a prerequisite for evidence-based shared decision-making, yet the investigators in the majority of the studies omitted to include these important patient-preferred outcomes. In the few trials where PROs were considered, these assessments were made based on non-validated and therefore questionably reliable instruments. Furthermore, none of the PRO assessment tools that were used met most or all of the recommended criteria based on the 'Checklist for describing and assessing PROs in Clinical Trials' (see Chapter 17.6.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)).

Imprecision of the results

In only a few instances was the effect estimate tightly bound by the confidence interval and consequently imprecision was the most frequent reason for downgrading the quality of the evidence for different outcomes per comparison. Imprecision was predominantly due to the small sample size in the studies.

Inconsistency of the results

Most of the comparisons were evaluated in single studies, which did not permit assessments of consistency of the results across studies for the majority of treatments. In those studies where outcome data could be pooled, this was often accompanied by substantial heterogeneity for one or more outcomes, such as in the following comparisons: 'flutamide versus metformin' (comparison 110) and 'finasteride versus flutamide' (comparison 111). In the comparison of flutamide versus metformin, which showed flutamide to be more effective, this could have been associated with the longer treatment duration of flutamide in one of the studies. In the other comparison of 'finasteride versus flutamide' we could not find a plausible explanation for the heterogeneity. Although not pooled, the results on the effectiveness of gonadotropin-releasing analogues for reducing hirsutism were also not consistent. In some comparisons they seemed more effective than in others, however this treatment option is no longer widely used for the treatment of hirsutism.

Publication bias

Since none of the comparisons involved 10 or more studies, formal assessment of publication bias was not feasible. However, we did identify 33 duplicate reports of the same study data in our searches (see under Results of the search).

Potential biases in the review process

We made concerted efforts to limit bias in the review process by making certain that an exhaustive and comprehensive search had been undertaken for potentially eligible studies. The authors assessed the eligibility of studies for inclusion in this review and carried out the data extraction independently, thereby minimising the potential for additional bias beyond that detailed in the 'Risk of bias' tables ('Characteristics of included studies'). We took care to identify duplicate publication of data or co-publication of same-study data. The incompleteness of some of the trial data and our inability to retrieve certain study details or to resolve ambiguities in the reports may have contributed to some bias in their assessment, but where these conditions occurred, this was explicitly stated in the text of our review. To minimise the risk of language bias on the identification and selection of studies for inclusion in our systematic review, we ensured that any studies that were not in the English language were translated so that they could be assessed for eligibility.

Agreements and disagreements with other studies or reviews

Our comprehensive searches for other relevant studies, reviews, and clinical guidelines included a number of clinical references and sources for guidelines and systematic reviews: Agency for Healthcare Research and Quality (http://www.ahrq.gov/), DynaMed (https://dynamed.ebscohost.com/), National Guidelines Clearinghouse (http://www.guideline.gov/), National Institute for Health and Clinical Excellence (http://www.nice.org.uk/), Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk/index.html), Endocrine Society (http://www.endocrine.org/), UK Database of Uncertainties about the Effects of Treatments (http://www.library.nhs.uk/duets/), and UpToDate (http://www.uptodate.com/home).

We identified a number of relevant intervention-specific systematic reviews of randomised controlled trials in addition to several more broader, overarching clinical guidelines, many of which were underpinned by systematic and fully inclusive searches for evidence. This clinical topic also attracted a large number of narrative reviews, which had been published over the last 10 years but were of variable and less robust methodological quality, more especially in their approach to searching for, and critical appraisal of, relevant studies (see Table 5 for an overview on reviews). Several Cochrane

reviews partially overlapped our inclusion criteria of types of participants and interventions or addressed our outcomes or all of these (see below).

Although we had some concerns about the methodological quality of some of these studies and reviews, in general the direction of their conclusions was in agreement with our findings. The overriding recommendations were that, to obtain the most beneficial or desired effect, combination therapies should be used in the management of hirsutism. In general OCPs were considered to be the first line of treatment for mild hirsutism, and in the absence of a satisfactory end result or in case of moderate to severe hirsutism, antiandrogens or 5α-reductase inhibitors were to be added (Blume-Peytavi 2013; Castelo-Branco 2010; Escobar-Morreale 2012; Legro 2013; Martin 2008). In the systematic review of Swiglo 2008 the investigators concluded: "weak evidence suggests antiandrogens are mildly effective agents for the treatment of hirsutism", which was broadly in agreement with our conclusions. Most of the reviews emphasised that it may take at least six to 12 months for oral treatment to demonstrate a noticeable effect (Blume-Peytavi 2013; Escobar-Morreale 2010; Paparodis 2011; Rosenfield 2005), and up to two years to achieve the optimum effect (Azziz 2003). There was a general consensus that in view of the possible time lag between treatment and effect, pharmacological therapy should be combined with cosmetic procedures such as bleaching, shaving, waxing, and plucking or more permanent hair removal with electrolysis or light-based therapies (intense pulsed light therapy or laser) or both (Blume-Peytavi 2013; Castelo-Branco 2010; Escobar-Morreale 2010; Lumachi 2010; Martin 2008).

Insulin sensitisers are often recommended for women with polycystic ovary syndrome (PCOS) and insulin resistance to improve insulin sensitivity, decrease androgen production, and raise the levels of SHBG, which ultimately might lead to an improvement of hirsutism. The conclusions in the Cosma 2008 review were in agreement with our review that insulin sensitisers have limited or no important benefit on hirsutism in women. We found no evidence to indicate that lifestyle modification was an effective treatment approach for hirsutism, which was confirmed in a further review (Domecq 2013). However, there was general agreement among several of these reviews that for other potential risk factors associated with PCOS (e.g. cardiovascular disease and metabolic dysfunction) lifestyle measures, which included exercise and hypocaloric diets, should be advised for overweight women (Escobar-Morreale 2012; Koulouri 2009; Legro 2013; Pasquali 2013).

Gonadotropin-releasing hormone analogue therapy is no longer widely recommended because it causes symptoms of menopause including hot flushes, leads to bone loss, and is expensive (Blume-Peytavi 2008; Brodell 2010; Koulouri 2008).

Cochrane reviews

Several other Cochrane reviews have evaluated the effects of interventions in hirsute women (Brown 2009; Costello 2007; Farquhar 2012; Moran 2011; Tang 2012; van der Spuy 2003), however our attempts to draw comparisons between this review and these other reviews presented a number of challenges. There was a level of disagreement over specific methodological issues and some aspects of review conduct. These disagreements included how judgements were made by the review authors in the selection of studies, and in their 'Risk of bias' assessments for specific domains. In a number of instances these 'Risk of bias' assessments were not presented with explicit support for the individual judgements. We were also at variance with some of the approaches used in data collection or the subsequent analyses and reporting of those data. There was a degree of variability in how outcome data were reported in these reviews, i.e. change scores in some as opposed to comparisons of final values for key outcomes in others, and whilst the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (see Chapter 9.4.5.2) (Higgins 2011) are not prescriptive, they indicate that analyses based on change scores are likely to be more efficient and more powerful than final value scores.

Our conclusions on the effect of spironolactone for hirsutism were similar to those reported in Brown 2009, although we note some disagreement with the studies that had been included as well as excluded and with several of the judgements of risk of bias for some of the domains in the selected studies.

In the Costello 2007 systematic review, insulin-sensitising drugs were compared with the combined oral contraceptive pill for hirsutism, as well as acne and risk of diabetes, cardiovascular disease, and endometrial cancer in participants with polycystic ovary syndrome. We judged that three out of six of the studies included in the review had unusable or potentially unreliable data, because the primary report was either unclear about how many women were hirsute, or there were no separate data available for hirsute women, or the drop-out rate exceeded 40% (Cibula 2005; Morin-Papunen 2000; Morin-Papunen 2003) (see Table 3). In the remaining three studies, Elter 2002, Harborne 2003, and Rautio 2005, it was not possible to compare results for the studies between the reviews as we had calculated changes from baseline for outcomes such as Ferriman-Gallwey scores in our comparisons, whilst Costello 2007 reported end values.

We only shared two studies with the Cochrane review of Farquhar 2012, which focused on ovulation induction rather than hirsutism. Although we had several studies in common, hirsutism was not an outcome in Moran 2011. The effectiveness of insulin-sensitising drugs on improving reproductive outcomes and metabolic parameters for women with PCOS was covered in Tang 2012. We had discordant views on the judgements made for 'Risk of bias' assessments in several of the domains in the 11 studies common to both reviews. This disagreement could be explained in part by the fact that we had a measure of success in contacting the research investigators in these 11 studies, which allowed us to fill in many of the missing trial details that were not adequately addressed in

Tang 2012. We had the most overlap in terms of type of participants and intervention and number of shared studies with van der Spuy 2003 (which is being updated), in which the review authors examined the effects of cyproterone acetate in hirsutism, but we identified numerous disagreements with the studies selected for inclusion and in the review authors judgements for the 'Risk of bias' assessments in several of those studies.

Guidelines

The limited number of topic-specific clinical guidelines covering hirsutism was most likely because it is a clinical condition that is often covered by broader themes in endocrinology, e.g. polycystic ovary syndrome, hyperandrogenism, the effects of insulin sensitisers, or lifestyle modification programmes. The development process as reported in all of these guidelines involved a systematic search of the literature, assessment of the selected studies by an expert panel, and in a few instances included recommendations based on the GRADE approach. Although the developers of several of these guidelines provided the strength of recommendations, i.e. 'strong - we recommend', there was often insufficient clarity in reporting of how judgements were made as to which factors decreased or increased the quality level of a body of evidence. Possible factors that should be considered for downgrading or upgrading of the quality of evidence have been specified by GRADE (see Chapter 12.2 Table 12.2 in the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). A more detailed reporting of how and on what basis these decisions were made by the guideline developers would most likely provide increased transparency and add to the robustness of the process of guideline development. The 'Summary of findings' tables we present in this review provide a more complete report of these ratings and supporting reasons for all important outcomes, both desirable and undesirable, and the corresponding illustrative risk. We note that two clinical practice guidelines developed by the Endocrine Society Task Force on Hirsutism (http://www.endocrine.org/) were well conducted in a robust systematic way and used the GRADE approach to assess the quality of evidence and to make subsequent recommendations (Legro 2013; Martin 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Treatment should aim to remove the unwanted hairs, reduce or completely inhibit growth of new hairs, correct hormonal imbalances, and improve the self image, self esteem, and quality of life of the affected woman. To achieve these goals the treatment approach will need to encompass not only pharmacological therapies but also cosmetic procedures and lifestyle modification, as well as methods addressing the psychological support required to enhance individual coping mechanisms (Blume-Peytavi 2011; Blume-Peytavi 2013; Brodell 2010; Martin 2008). Our conclusions are supported by studies with a duration of between six and 12 months.

The effectiveness of oral contraceptives (OCPs), in particular those containing ethinyl estradiol 35 µg combined with cyproterone acetate 2 mg and ethinyl estradiol 30 µg combined with desogestrel 0.15 mg, was supported by low quality evidence. OCPs, preferentially those with antiandrogenic activity, can be considered as a possible first line treatment approach for mild hirsutism.

Among the antiandrogens both flutamide 250 mg twice a day as well as spironolactone 100 mg per day appeared to be effective and safe, although we rated the quality of the evidence as low to very low. Finasteride 5 mg per day showed inconsistent results for its effectiveness in the different comparisons, and therefore no firm conclusion can be made regarding this treatment. In addition, as the side effects of these antiandrogen treatments and finasteride are well known, these should be taken into account in any clinical decision-making.

Although we were unable to pool data for the effects of OCP combined with cyproterone acetate, this combination appeared to be more effective in reducing hirsutism. We were unable to draw conclusions on the effects of other combinations of OCPs, i.e. with flutamide, spironolactone, or finasteride versus OCPs only to see if these additions would result in a more beneficial effect on hirsutism. The inability to pool data was largely due to the wide diversity between treatment arms for these comparisons and because most of the comparisons examined one combination therapy against another different combination therapy. It should be emphasised that all antiandrogens as well as finasteride carry the risk of feminisation of the male foetus and should therefore always be combined with effective contraception. Hirsute women who wish to conceive can only be treated safely with cosmetic procedures.

Out of the insulin sensitisers, there was evidence rated as low quality that metformin was not effective in the treatment of hirsutism, but this does not mean that it has no therapeutic value in the treatment of overweight women with polycystic ovary syndrome (PCOS) and hyperinsulinaemia.

Although the gonadotropin-releasing hormone (GnRH) analogues did not show consistent results in reducing hirsutism they do have significant side effects such as hot flushes, premature menopausal symptoms, and bone loss. Consequently there would appear to be no therapeutic advantage with this category of drugs over OCPs and antiandrogens or finasteride.

Evidence was lacking to support the effect of lifestyle modification on the improvement of hirsutism and we did not identify any randomised controlled trials addressing cosmetic procedures for the treatment of hirsutism.

Clinical decision-making on the choice of treatment for hirsutism should be based on high-level evidence if it is available, but in the absence of such evidence for any other specific intervention, these decisions should continue to be guided by clinical experience and peoples' individual characteristics and preferences until further evidence for these other interventions becomes available. The appropriate monitoring of patients both clinically and biochemically while on therapy is important. Hirsute women are typically otherwise healthy and the risks and benefits of each therapeutic option must be carefully considered and discussed with them. In view of the fact that it may take six to 12 months before any treatment effect can be noticed, alternative and interim measures, including coping strategies and provision of psychological support as well as cosmetic measures, should also be integrated into the decision-making process.

Implications for research

This review covers a wide range of treatments used for the treatment of hirsutism and although we were able to include 157 studies, only very few studies were well designed and rigorously conducted and reported. A minority of the studies addressed patient-reported outcomes such as the participants' assessment of improvement of hirsutism, change in health-related quality of life, and adverse events, but these were frequently inadequately reported.

There is an urgent need for high-quality, well-designed, and rigorously reported studies of head-to-head trials examining OCPs combined with an antiandrogen or a 5α-reductase inhibitor against OCP monotherapy, as well as the different antiandrogens and 5α-reductase inhibitors against each other.

A major area for improvement would be in the standardisation of outcome reporting in any future research. Outcomes collected in future trials should be primarily based on a standardised scale of the participant's assessment of the treatment efficacy, and they should also have a greater emphasis on changes in quality of life as a result of the interventions. The minimal clinically important difference should be established to interpret the outcome data, and to ascertain if a treatment leads to a clinically meaningful and relevant reduction of hirsutism and improvement of quality of life.

Follow-up studies addressing the sustainability of hair reduction after discontinuation of treatment should be taken into account as this constitutes an important outcome for participants.

Since measurable hyperandrogaenemia and body mass index (BMI) do not always correlate with the degree of hirsutism, it may also be that certain forms of treatment have better efficacy in some women compared to others depending upon their baseline characteristics. Therefore, subgroup analyses addressing baseline characteristics might also be appropriate.

Future randomised controlled trials must be well-designed, well-conducted, and adequately delivered, with subsequent reporting including high-quality descriptions of all aspects of methodology. Rigorous reporting needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement, and this will enable appraisal and interpretation of results, and accurate judgements to be made about the risk of bias and the overall quality of the evidence. Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995). Adherence to guidelines, such as the CONSORT statement, would help ensure complete reporting.

For further research recommendations based on the EPICOT (evidence, population, intervention, comparison, outcomes, and time) format (Brown 2006), see Table 6.

ACKNOWLEDGEMENTS

The Cochrane Skin Group editorial base wishes to thank Sam Gibbs who was the Key Editor for this protocol; Matthew Grainge and Philippa Middleton who were the Statistical and Methods Editors, respectively; the clinical referee, Ulrike Blume-Peytavi; and the consumer referee, Ankur Barua. We would like to acknowledge the help we have received in the translation of studies into English by Dr Malgorzata Bala of Jagiellonian University Medical College, Krakow Poland, Esra Qadami, medical student in AMA College of Medicine International University of Bahrain, Lenka Pereira-Bouda, nuclear physician, Leiden University Medical Centre and Rijnland Hospital, Leiden and Leiderdorp respectively, the Netherlands, and Sandro Pasquali of the Meta-Analysis Unit, Department of Surgery, Oncology and Gastroenterology University of Padova, Padova, Italy.

REFERENCES

References to studies included in this review

Ahmad 2008 *{published data only}*

Ahmad J, Shukla N, Khan AR, Ahmed F, Siddiqui MA. Comparison of metabolic effects of metformin and rosiglitazone in the management of polycystic ovary syndrome (PCOS): a prospective, parallel, randomized, open-label study. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2008;**2**(1):37–46. [EMBASE: 2008061564]

Aigner 2009 *{published data only}*

Aigner E, Bachofner N, Klein K, De Geyter C, Hohla F, Patsch W, et al. Retinol-binding protein 4 in polycystic ovary syndrome-association with steroid hormones and response to pioglitazone treatment. *Journal of Clinical Endocrinology and Metabolism* 2009;**94**(4):1229–35. [PUBMED: 19158194]

Akalin 1991 *{published data only}*

Akalin S. Effects of ketoconazole in hirsute women. *Acta Endocrinologica* 1991;**124**(1):19–22. [PUBMED: 1825737]

Al-Khawajah 1998 *{published data only}*

Al-Khawajah MM. Finasteride for hirsutism: a dose finding study. *Saudi Medical Journal* 1998;**19**(1):19–21. [EMBASE: 1998139572]

Allen 2005 *{published data only}*

Allen HF, Mazzoni C, Heptulla RA, Murray MA, Miller N, Koenigs L, et al. Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. *Journal of Pediatric Endocrinology & Metabolism* 2005;**18**(8): 761–8. [PUBMED: 16200842]

Ashrafinia 2009 *{published data only}*

Ashrafinia M, Hosseini R, Moini A, Eslami B, Asgari Z. Comparison of metformin treatment and laparoscopic ovarian diathermy in patients with polycystic ovary syndrome. *International Journal of Gynaecology & Obstetrics* 2009;**107**(3):236–9. [PUBMED: 19729161]

Azziz 1995 *{published data only}*

Azziz R, Ochoa TM, Bradley EL Jr, Potter HD, Boots LR. Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *Journal of Clinical Endocrinology & Metabolism* 1995;**80** (12):3406–11. [PUBMED: 8530573]

Azziz 2001 *{published data only}*

Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *Journal of Clinical Endocrinology & Metabolism* 2001;**86**(4):1626–32. [PUBMED: 11297595]

Badawy 2009b *{published data only}*

* Badawy A, Khiary M, Ragab A, Hassan M, Sherief L. Ultrasound-guided transvaginal ovarian needle drilling (UTND) for treatment of polycystic ovary syndrome: a randomized controlled trial. *Fertility & Sterility* 2009;**91**(4): 1164–7. [PUBMED: 18342858]

Badawy A, Khiary M, Ragab A, Sherif L. Ultrasound-guided transvaginal ovarian needle drilling (UTND) for treatment of polycystic ovary syndrome: a randomized controlled trial. Conference: 25th Annual Meeting of the European Society of Human Reproduction and Embryology, ESHRE Amsterdam Netherlands. *Molecular Human Reproduction* 2009;**24**(Suppl 1):i179. [EMBASE: 70197442]

Banaszewska 2007 *{published data only}*

* Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover trial. *Journal of Clinical Endocrinology & Metabolism* 2007;**92**(2):456–61. [PUBMED: 17105841]

Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Simvastatin improves biochemical parameters in women with polycystic ovary syndrome: results of a prospective, randomized trial. *Fertility & Sterility* 2006;**85**(4):996–1001. [PUBMED: 16580386]

Banaszewska 2011 *{published data only}*

Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: prospective randomized trial. *Journal of Clinical Endocrinology & Metabolism* 2009;**94** (12):4938–45. [PUBMED: 19890022]

* Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Effects of simvastatin and metformin on polycystic ovary syndrome after six months of treatment. *Journal of Clinical Endocrinology & Metabolism* 2011;**96**(11):3493–501. [PUBMED: 21865358]

Barth 1991 *{published data only}*

Barth JH, Cherry CA, Wojnarowska F, Dawber RP. Cyproterone acetate for severe hirsutism: results of a double-blind dose-ranging study. *Clinical Endocrinology* 1991;**35**(1):5–10. [PUBMED: 1832346]

Battaglia 2010 *{published data only}*

Battaglia C, Mancini F, Fabbri R, Persico N, Busacchi P, Facchinetti F, et al. Polycystic ovary syndrome and cardiovascular risk in young patients treated with drospirenone-ethinylestradiol or contraceptive vaginal ring. A prospective, randomized, pilot study. *Fertility & Sterility* 2010;**94**(4):1417–25. [PUBMED: 19591981]

Batukan 2007 *{published data only}*

Batukan C, Muderris II, Ozcelik B, Ozturk A. Comparison of two oral contraceptives containing either drospirenone or cyproterone acetate in the treatment of hirsutism. *Gynecological Endocrinology* 2007;**23**(1):38–44. [PUBMED: 17484511]

Bayhan 2000 *{published data only}*

Bayhan G, Bahçeci M, Demirkol T, Ertem M, Yalinkaya A, Erden AC. A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism.

Clinical & Experimental Obstetrics & Gynecology 2000;**27**(3-4):203–6. [PUBMED: 11214952]

Bayram 2002 *{published data only}*
Bayram F, Müderris II, Güven M, Keletimur F. Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2002;**147**(4):467–71. [PUBMED: 12370107]

Beigi 2004 *{published data only}*
Beigi A, Sobhi A, Zarrinkoub F. Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *International Journal of Gynaecology & Obstetrics* 2004;**87**(1):29–33. [PUBMED: 15464773]

Belisle 1986 *{published data only}*
Belisle S. Cyproterone acetate in severe hirsutism: results of an ongoing multicentered study by the Canadian Committee for Fertility Research. *Archives of Gynecology* 1985;**237**(1 Suppl):199.
* Belisle S, Love EJ. Clinical efficacy and safety of cyproterone acetate in severe hirsutism: results of a multicentered Canadian study. *Fertility & Sterility* 1986;**46**(6):1015–20. [PUBMED: 2946604]

Bhattacharya 2012 *{published data only}*
Bhattacharya SM, Jha A. Comparative study of the therapeutic effects of oral contraceptive pills containing desogestrel, cyproterone acetate, and drospirenone in patients with polycystic ovary syndrome. *Fertility & Sterility* 2012;**98**(4):1053–9. [PUBMED: 22795636]

Breitkopf 2003 *{published data only}*
Breitkopf DM, Rosen MP, Young SL, Nagamani M. Efficacy of second versus third generation oral contraceptives in the treatment of hirsutism. *Contraception* 2003;**67**(5):349–53. [PUBMED: 12742556]

Brettenthaler 2004 *{published data only}*
Brettenthaler N, De Geyter C, Huber PR, Keller U. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2004;**89**(8):3835–40. [PUBMED: 15292314]

Brown 2009B *{published data only}*
Brown AJ, Setji TL, Sanders LL, Lowry KP, Otvos JD, Kraus WE, et al. Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. *Medicine & Science in Sports and Exercise* 2009;**41**(3):497–504. [PUBMED: 19204602]

Calaf 2007 *{published data only}*
Calaf J, López E, Millet A, Alcañiz J, Fortuny A, Vidal O, et al. Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *Journal of Clinical Endocrinology & Metabolism* 2007;**92**(9):3446–52. [PUBMED: 17566093]

Carmina 1994 *{published data only}*
Carmina E, Janni A, Lobo RA. Physiological estrogen replacement may enhance the effectiveness of the gonadotropin-releasing hormone agonist in the treatment of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1994;**78**(1):126–30. [PUBMED: 8288696]

Carmina 1998 *{published data only}*
Carmina E, Lobo RA. The addition of dexamethasone to antiandrogen therapy for hirsutism prolongs the duration of remission. *Fertility & Sterility* 1998;**69**(6):1075–9. [PUBMED: 9627295]

Carr 1995 *{published data only}*
Carr BR, Breslau NA, Givens C, Byrd W, Barnett-Hamm C, Marshburn PB. Oral contraceptive pills, gonadotropin-releasing hormone agonists, or use in combination for treatment of hirsutism: a clinical research center study. *Journal of Clinical Endocrinology & Metabolism* 1995;**80**(4):1169–78. [PUBMED: 7714086]

Cedeno 1990 *{published data only}*
Cedeno J, Mendoza SG, Velazquez E, Nucete H, Speirs J, Glueck CJ. Effect of ketoconazole on plasma sex hormones, lipids, lipoproteins, and apolipoproteins in hyperandrogenic women. *Metabolism: Clinical & Experimental* 1990;**39**(5):511–7. [PUBMED: 2139916]

Cibula 2005 *{published data only}*
Cibula D, Fanta M, Vrbikova J, Stanicka S, Dvorakova K, Hill M, et al. The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenaemia, SHBG and lipids in PCOS patients. *Human Reproduction* 2005;**20**(1):180–4. [PUBMED: 15576394]

Cicek 2003 *{published data only}*
Çiçek MN, Bala A, Celik C, Akyürek C. The comparison of clinical and hormonal parameters in PCOS patients treated with metformin and GnRH analogue. *Archives of Gynecology & Obstetrics* 2003;**268**(2):107–12. [PUBMED: 12768300]

Ciotta 1995 *{published data only}*
Ciotta L, Cianci A, Calogero AE, Palumbo MA, Marletta E, Sciuto A, et al. Clinical and endocrine effects of finasteride, a 5 alpha-reductase inhibitor, in women with idiopathic hirsutism. *Fertility & Sterility* 1995;**64**(2):299–306. [PUBMED: 7615107]

Ciotta 2001 *{published data only}*
Ciotta L, Calogero AE, Farina M, De Leo V, La Marca A, Cianci A. Clinical, endocrine and metabolic effects of acarbose, an alpha-glucosidase inhibitor, in PCOS patients with increased insulin response and normal glucose tolerance. *Human Reproduction* 2001;**16**(10):2066–72. [PUBMED: 11574493]

Ciotta 2012 *{published data only}*
Ciotta L, Formuso C, Pagano I, Stracquadanio M. Myo-inositol vs D-Chiro inositol in PCOS treatment. *International Journal of Gynecology & Obstetrics* 2012;**119**(Suppl 3):S545. [EMBASE: 70906140]

Ciotta 2012B *{published data only}*
Ciotta L, Stracquadanio M, Pagano I, Formuso C, Leo S, Cianci A. D-Chiro-Inositol treatment in patients with polycystic ovary syndrome. *Giornale Italiano Di Ostetricia e Ginecologia* 2012;**34**(1):145–8. [EMBASE: 2012245049]

Consoli 1994 *{published data only}*
Consoli SM, Vexiau P, Consoli SG, Abramovici Y. Acceptance, tolerance and effects on quality of life of treatment of hirsute women with cyproterone acetate. Comparison of association with oral estradiol to association with transdermal estradiol. *Contraception, Fertilite, Sexualite* 1994;**22**(12):783–7. [EMBASE: 1995012638]

Couzinet 1986 *{published data only}*
Couzinet B, Le Strat N, Brailly S, Schaison G. Comparative effects of cyproterone acetate or a long-acting gonadotropin-releasing hormone agonist in polycystic ovarian disease. *Journal of Clinical Endocrinology & Metabolism* 1986;**63**(4): 1031–5. [PUBMED: 2943752]

Crave 1995 *{published data only}*
Crave JC, Fimbel S, Lejeune H, Cugnardey N, Déchaud H, Pugeat M. Effects of diet and metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women. *Journal of Clinical Endocrinology & Metabolism* 1995;**80**(7):2057–62. [PUBMED: 7608255]

Creatsas 1993 *{published data only}*
Creatsas G, Hassan E, Deligeoroglou E, Tolis G, Aravantinos D. Treatment of polycystic ovarian disease during adolescence with ethinylestradiol/cyproterone acetate versus a D-Tr-6-LHRH analog. *International Journal of Gynaecology & Obstetrics* 1993;**42**(2):147–53. [PUBMED: 7901064]

Creatsas 2000 *{published data only}*
Creatsas G, Koliopoulos C, Mastorakos G. Combined oral contraceptive treatment of adolescent girls with polycystic ovary syndrome. Lipid profile. *Annals of the New York Academy of Sciences* 2000;**900**:245–52. [PUBMED: 10818412]

Cusan 1994 *{published data only}*
Cusan L, Dupont A, Gomez JL, Tremblay RR, Labrie F. Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertility & Sterility* 1994;**61**(2):281–7. [PUBMED: 8299783]

De Leo 2000 *{published data only}*
De Leo V, Fulghesu AM, la Marca A, Morgante G, Pasqui L, Talluri B, et al. Hormonal and clinical effects of GnRH agonist alone, or in combination with a combined oral contraceptive or flutamide in women with severe hirsutism. *Gynecological Endocrinology* 2000;**14**(6):411–6. [PUBMED: 11228061]

Dereli 2005 *{published data only}*
Dereli D, Dereli T, Bayraktar F, Ozgen AG, Yilmaz C. Endocrine and metabolic effects of rosiglitazone in non-obese women with polycystic ovary disease. *Endocrine Journal* 2005;**52**(3):299–308. [PUBMED: 16006724]

Dixon 1991 *{published data only}*
Dixon JE, Hicks BH, Chapman MG. Hirsutography: Photographic measurement of linear hair growth in hirsute women during comparison of anti-androgen treatments. *Journal of Obstetrics & Gynaecology* 1991;**11**(1):63–7. [EMBASE: 1991099168]

Eisenhardt 2006 *{published data only}*
Eisenhardt S, Schwarzmann N, Henschel V, Germeyer A, von Wolff M, Hamann A, et al. Early effects of metformin in women with polycystic ovary syndrome: a prospective randomized, double-blind, placebo-controlled trial. *Journal of Clinical Endocrinology & Metabolism* 2006;**91**(3):946–52. [PUBMED: 16352680]

Elkind-Hirsch 1995 *{published data only}*
Elkind-Hirsch KE, Anania C, Mack M, Malinak R. Combination gonadotropin-releasing hormone agonist and oral contraceptive therapy improves treatment of hirsute women with ovarian hyperandrogenism. *Fertility & Sterility* 1995;**63**(5):970–8. [PUBMED: 7720941]

Elnashar 2006 *{published data only}*
Elnashar A, Abdelmageed E, Fayed M, Sharaf M. Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study. *Human Reproduction* 2006;**21**(7):1805–8. [PUBMED: 16543255]

Elter 2002 *{published data only}*
Elter K, Imir G, Durmusoglu F. Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. *Human Reproduction* 2002;**17**(7):1729–37. [PUBMED: 12093831]

Erenus 1994 *{published data only}*
Erenus M, Gürbüz O, Durmuoğ lu F, Demirçay Z, Pekin S. Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertility & Sterility* 1994;**61**(4):613–6. [PUBMED: 8150100]

Erenus 1996 *{published data only}*
Erenus M, Yücelten D, Gürbüz O, Durmuo ğ lu F, Pekin S. Comparison of spironolactone-oral contraceptive versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Fertility & Sterility* 1996;**66** (2):216–9. [PUBMED: 8690104]

Erenus 1997 *{published data only}*
Erenus M, Yücelten D, Durmuoğ lu F, Gürbüz O. Comparison of finasteride versus spironolactone in the treatment of idiopathic hirsutism. *Fertility & Sterility* 1997; **68**(6):1000–3. [PUBMED: 9418687]

Erkkola 1990 *{published data only}*
Erkkola R, Hirvonen E, Luikku J, Lumme R, Männikkö H, Aydinlik S. Ovulation inhibitors containing cyproterone acetate or desogestrel in the treatment of hyperandrogenic symptoms. *Acta Obstetricia et Gynecologica Scandinavica* 1990;**69**(1):61–5. [PUBMED: 2140663]

Esmaeilzadeh 2010 *{published data only}*
Esmaeilzadeh S, Ghorbani L, Sharbatdaran M, Bijani A, Sajadi P. Comparison of flutamide and metformin in overweight-obese women with polycystic ovary syndrome following a hypocaloric dieting. *Journal of Babol University of Medical Sciences* 2010;**12**(4):7–13. [EMBASE: 2011042010]

Falsetti 1992 *{published data only}*
Falsetti L, Pasinetti E, Chioda C, Grigolato PG. Treatment of moderate and severe hirsutism with a gonadotrophin-releasing hormone agonist. *Human Reproduction* 1992;**7**(6): 894. [EMBASE: 1992237168]

Falsetti 1994 *{published data only}*
Falsetti L, Pasinetti E. Treatment of moderate and severe hirsutism by gonadotropin-releasing hormone agonists in women with polycystic ovary syndrome and idiopathic hirsutism. *Fertility & Sterility* 1994;**61**(5):817–22. [PUBMED: 8174716]

Falsetti 1994B *{published data only}*
Falsetti L, Pasinetti E, Ceruti D. Gonadotropin-releasing hormone agonist (GnRH-A) in hirsutism. *Acta Europaea Fertilitatis* 1994;**25**(5):303–6. [PUBMED: 7660719]

Falsetti 1999 *{published data only}*
Falsetti L, Gambera A. Comparison of finasteride and flutamide in the treatment of idiopathic hirsutism. *Fertility & Sterility* 1999;**72**(1):41–6. [PUBMED: 10428146]
* Falsetti L, Gambera A, Legrenzi L, Iacobello C, Bugari G. Comparison of finasteride versus flutamide in the treatment of hirsutism. *European Journal of Endocrinology / European Federation of Endocrine Societies* 1999;**141**(4):361–7. [PUBMED: 10526249]

Farina 2006 *{published data only}*
Farina M, Ciotta L, Palumbo M, Leo V, Morgante G, Cianci A. Effectiveness of an oral contraceptive containing ethinyl-estradiol combined with drospirenone in the treatment of symptomatic hyperandrogenism [Efficacica clinica di un contraccettivo orale contenente etinilestradiolo e drospirenone nel trattamento dell'iperandrogenismo sintomatico]. *Italian Journal of Gynaecology & Obstetrics* 2006;**18**(1):18–31. [EMBASE: 2008312396]

Farquhar 2002 *{published data only}*
* Farquhar CM, Williamson K, Gudex G, Johnson NP, Garland J, Sadler L. A randomized controlled trial of laparoscopic ovarian diathermy versus gonadotrophin therapy for women with clomiphene resistant polycystic ovarian syndrome. *Fertility & Sterility* 2002;**78**(2):404–11. [EMBASE: 2002275330]
Mohiuddin S, Bessellink D, Farquhar C. Long-term follow up of women with laparoscopic ovarian diathermy for women with clomiphene-resistant polycystic ovarian syndrome. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2007;**47**(6):508–11. [PUBMED: 17991119]

Fruzzetti 1999 *{published data only}*
Fruzzetti F, Bersi C, Parrini D, Ricci C, Genazzani AR. Treatment of hirsutism: comparisons between different antiandrogens with central and peripheral effects. *Fertility & Sterility* 1999;**71**(3):445–51. [PUBMED: 10065780]

Fruzzetti 2010 *{published data only}*
Daria P, Fruzzetti, Genazzani AR. Metabolic effects of of 3 mg drospirenone plus 20 mg ethinyl estradiol alone or combined with metformin or cyproterone acetate. XVI International Congress of ISPOG Venezia, Italy October 28-30, 2010. *Journal of Psychosomatic Obstetrics & Gynecology* 2010;**31**:78. [EMBASE: 70302184]
* Fruzzetti F, Perini D, Lazzarini V, Parrini D, Gambacciani M, Genazzani AR. Comparison of effects of 3 mg drospirenone plus 20 ug ethinyl estradiol alone or combined with metformin or cyproterone acetate on classic metabolic cardiovascular risk factors in nonobese women with polycystic ovary syndrome. *Fertility & Sterility* 2010;**94**(5): 1793–8. [PUBMED: 19931080]

Gambineri 2005 *{published data only}*
Gambineri A, Patton L, De Iasio R, Cantelli B, Cognini GE, Filicori M, et al. Efficacy of octreotide-LAR in dieting women with abdominal obesity and polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2005;**90**(7):3854–62. [PUBMED: 15827099]

Gambineri 2006 *{published data only}*
* Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, et al. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *Journal of Clinical Endocrinology & Metabolism* 2006; **91**(10):3970–80. [PUBMED: 16868063]
Gambineri A, Pelusi C, Genghini S, Morselli-Labate AM, Cacciari M, Pagotto U, et al. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clinical Endocrinology* 2004;**60**(2):241–9. [PUBMED: 14725687]

Ganie 2004 *{published data only}*
Ganie MA, Khurana ML, Eunice M, Gupta N, Gulati M, Dwivedi SN, et al. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. *Journal of Clinical Endocrinology & Metabolism* 2004;**89**(6):2756–62. [PUBMED: 15181054]

Ghosh 2008 *{published data only}*
Ghosh D, Murphy C, Elsheikh M. A randomised trial comparing a low carbohydrate diet and nutrient-balanced low glycaemic index diet on body weight, hyperandrogenism and cardiovascular risk factors in women with polycystic ovary syndrome (PCOS) presented at Society for Endocrinology BES 2008, 7-10 April 2008, Harrogate, UK. *Endocrine Abstracts* 2008;**15**:P279.

Grant 2010 *{published data only}*
Grant P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. *Phytotherapy Research* 2010;**24**(2):168–8. [PUBMED: 19585478]

Hamzavi 2007 *{published data only}*

Hamzavi I, Tan E, Shapiro J, Lui H. A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *Journal of the American Academy of Dermatology* 2007;**57**(1):54–9. [PUBMED: 17270315]

Harborne 2003 *{published data only}*

Harborne L, Fleming R, Lyall H, Norman J. Metformin or Dianette treatment of hirsutism with polycystic ovarian syndrome. *Human Reproduction* 2002;**17**(1):45.

* Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2003;**88**(9):4116–23. [PUBMED: 12970273]

Harborne L, Norman J, Lyall H, Flemming R. Metformin may be more effective than Dianette in the treatment of hirsutism in women with polycystic ovary syndrome. *Human Reproduction* 2003;**18**(Suppl 1):173.

Heiner 1995 *{published data only}*

Heiner JS, Greendale GA, Kawakami AK, Lapolt PS, Fisher M, Young D, et al. Comparison of a gonadotropin-releasing hormone agonist and a low dose oral contraceptive given alone or together in the treatment of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1995;**80**(12):3412–8. [PUBMED: 8530574]

Hoeger 2004 *{published data only}*

Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertility & Sterility* 2004;**82**(2): 421–9. [PUBMED: 15302293]

Hoeger 2008 *{published data only}*

Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *Journal of Clinical Endocrinology & Metabolism* 2008;**93**(11):4299–306. [PUBMED: 18728175]

Holdaway 1985 *{published data only}*

Holdaway IM, Croxson MS, Ibbertson HK, Sheehan A, Knox B, France J. Cyproterone acetate as initial treatment and maintenance therapy for hirsutism. *Acta Endocrinologica* 1985;**109**(4):522–9. [PUBMED: 2930987]

Huber 1985 *{published data only}*

Huber J, Schmidt J, Spona J. Hirsutism therapy by a single 300 mg im administration of cyproterone acetate vs 1000 mg oral treatment. *Archives of Gynecology* 1985;**237**(Suppl 1):200.

Ibáñez 2002 *{published data only}*

Ibáñez L, Valls C, Ferrer A, Ong K, Dunger DB, De Zegher F. Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *Journal of Clinical Endocrinology & Metabolism* 2002;**87**(6):2870–4. [PUBMED: 12050266]

Ibáñez 2003 *{published data only}*

Ibáñez L, Ong K, Ferrer A, Amin R, Dunger D, de Zegher F. Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *Journal of Clinical Endocrinology & Metabolism* 2003;**88**(6):2600–6. [PUBMED: 12788862]

Ibáñez 2009 *{published data only}*

Ibáñez L, López-Bermejo A, Díaz M, Enríquez G, Del Río L, De Zegher F. Low-dose pioglitazone, flutamide, metformin plus an estro-progestagen for non-obese young women with polycystic ovary syndrome: increasing efficacy and persistent safety over 30 months. *Gynecological Endocrinology* 2010;**26** (12):869–73. [PUBMED: 20500100]

Ibáñez L, López-Bermejo A, Díaz M, Enríquez G, Valls C, de Zegher F. Pioglitazone (7.5 mg/day) added to flutamide-metformin in women with androgen excess: additional increments of visfatin and high molecular weight adiponectin. *Clinical Endocrinology* 2008;**68**(2):317–20. [PUBMED: 18031315]

* Ibáñez L, López-Bermejo A, Díaz M, Enríquez G, del Río L, de Zegher F. Low-dose pioglitazone and low-dose flutamide added to metformin and oestro-progestagens for hyperinsulinaemic women with androgen excess: add-on benefits disclosed by a randomized double-placebo study over 24 months. *Clinical Endocrinology* 2009;**71**(3):351–7. [PUBMED: 19018783]

Ibáñez L, López-Bermejo A, del Rio L, Enríquez G, Valls C, de Zegher F. Combined low-dose pioglitazone, flutamide, and metformin for women with androgen excess. *Journal of Clinical Endocrinology & Metabolism* 2007;**92**(5):1710–4. [PUBMED: 17299064]

Ibáñez 2011B *{published data only}*

Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Early metformin therapy (age 8-12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. *Journal of Clinical Endocrinology & Metabolism* 2011;**96**(8):E1262–7. [PUBMED: 21632811]

Ibáñez 2012 *{published data only}*

Díaz M, Chacón MR, López-Bermejo A, Maymó-Masip E, Salvador C, Vendrell J, et al. Ethinyl estradiol-cyproterone acetate versus low-dose pioglitazone-flutamide-metformin for adolescent girls with androgen excess: divergent effects on CD163, TWEAK receptor, ANGPTL4, and LEPTIN expression in subcutaneous adipose tissue. *Journal of Clinical Endocrinology & Metabolism* 2012;**97**(10):3630–8. [PUBMED: 22791755]

Ibáñez L, Diaz M, Lopez-Bermejo A, Salvador C, De Zegher F. Ethinylestradiol-cyproterone acetate vs pioglitazone-flutamide-metformin in adolescent girls with androgen excess. *Endocrine Reviews* 2011;**32**(3 Meeting Abstracts): P2–247.

Ibáñez L, Diaz M, Lopez-Bermejo A, Salvador C, De Zegher F. Ethinylestradiol-cyproterone acetate vs pioglitazone-flutamide-metformin in adolescent girls with androgen

excess. 50th Annual Meeting of the European Society for Paediatric Endocrinology, ESPE 2011 Glasgow United Kingdom. Conference Start: 20110925 Conference End: 20110928. *Hormone Research in Paediatrics* 2011;**76**(Suppl 2):93. [EMBASE: 70570644]

Ibáñez L, Diaz M, Sebastiani G, Sánchez-Infantes D, Salvador C, Lopez-Bermejo A, et al. Treatment of androgen excess in adolescent girls: ethinyl estradiol-cyproterone acetate versus low-dose pioglitazone-flutamide-metformin. *Journal of Clinical Endocrinology & Metabolism* 2011;**96**(11):3361–6. [PUBMED: 21865363]

* Ibáñez L, Díaz M, Chacón MR, López-Bermejo, Maymo-Masip E, Salvador C, et al. Ethinyloestradiol-cyproteroneacetate versus low-dose pioglitazone-flutamide-metformin for adolescent girls with androgen excess: divergent effects over 1 year. *Hormone Research in Paediatrics* 2012;**78**(Suppl 1):95. [EMBASE: 70896314]

Iraji 2005 *{published data only}*

Iraji F, Karbasioun S, Aminorroaya A. Topical finasteride in hirsutism: a double blind randomized clinical trial on adult women. *Journal of Research in Medical Sciences* 2005;**10**(6):337–42. [EMBASE: 2005581713]

Jackson 2007 *{published data only}*

Jackson J, Caro JJ, Caro G, Garfield F, Huber F, Zhou W, et al. The effect of eflornithine 13.9% cream on the bother and discomfort due to hirsutism. *International Journal of Dermatology* 2007;**46**(9):976–81. [PUBMED: 17822506]

Javidnia 2003 *{published data only}*

Javidnia K, Dastgheib L, Mohammadi Samani S, Nasiri A. Antihirsutism activity of fennel (fruits of Foeniculum vulgare) extract. A double-blind placebo controlled study. *Phytomedicine* 2003;**10**(6-7):455–8. [PUBMED: 13678227]

Jedel 2011 *{published data only}*

Jedel E, Labrie F, Odén A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. *American Journal of Physiology, Endocrinology & Metabolism* 2011;**300**(1):E37–45. [PUBMED: 20943753]

Kaiser 1984 *{published data only}*

Kaiser E. Effect of a new hormonal contraceptive (Neo-Eunomin) in females with androgenization symptoms [Wirkung Eines Neuen Hormonalen Kontrazeptivums (Neo–Eunomin) Bei Frauen Mit Androgenisierungserscheinungen]. *Geburtshilfe Und Frauenheilkunde* 1984;**44**(10):651–5. [EMBASE: 1984246709]

Kaya 2010 *{published data only}*

Kaya C, Pabuccu R, Cengiz SD, Dünder I. Comparison of the effects of atorvastatin and simvastatin in women with polycystic ovary syndrome: a prospective, randomized study. *Experimental & Clinical Endocrinology & Diabetes* 2010;**118**(3):161–6. [PUBMED: 20146169]

Kelekci 2012 *{published data only}*

* Kelekci KH, Kelekci S, Yengel I, Gul S, Yilmaz B. Cyproterone acetate or drospirenone containing combined oral contraceptives plus spironolactone or cyproterone acetate for hirsutism: randomized comparison of three regimens. *Journal of Dermatological Treatment* 2012;**23**(3):177–83. [PUBMED: 21254871]

Kelekci KH, Kelekci S, Yengel R, Gul F, Ylmaz B. Comparison of the efficacy of three different regimens in the treatment of moderate and severe hirsutism. Conference: 8. Ulusal Jinekoloji ve Obstetrik Kongresi Carsamba Turkey. *Turk Jinekoloji ve Obstetrik Dernegi Dergisi* 2010;**7**:38. [EMBASE: 71042134]

Kelly 2002 *{published data only}*

Kelly CJ, Gordon D. The effect of metformin on hirsutism in polycystic ovary syndrome. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2002;**147**(2):217–21. [PUBMED: 12153743]

Kjøtrød 2004 *{published data only}*

Kjøtrød SB, von Düring V, Carlsen SM. Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study. *Human Reproduction* 2004;**19**(6):1315–22. [PUBMED: 15117902]

Kriplani 2009 *{published data only}*

Kriplani A, Thulkar J, Agrawal N, Kulshrestha V, Ammini AC, Kumar G. A comparative study of Diane-35 plus spironolactone and Diane-35 plus finasteride in cases of hirsutism and acne. *International Journal of Endocrinology and Metabolism* 2009;**7**(4):235–41.

Kriplani 2010 *{published data only}*

Kriplani A, Anurekha J, Agarwal N, Kulshrestha V, Kumar A, Ammini A. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs desogestrel on clinical and biochemical parameters in patients of polycystic ovarian syndrome. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S233.

* Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. *Contraception* 2010;**82**(2):139–46. [PUBMED: 20654754]

Lachnit-Fixson 1977 *{published data only}*

Lachnit-Fixson U, Kaufmann J. Therapy of androgenization symptoms: double blind study of an antiandrogen preparation (SH B 209 AB) against neogynon [Zur Beeinflussung von Androgenisierungserscheinungen: Doppelblindstudie eines cyproteronacetathaltigen Präparats (SH B 209 AM) gegen Neogynon]. *Medizinische Klinik* 1977;**72**(45):1922–6. [EMBASE: 1978213356]

Ladson 2011 *{published data only}*

Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, et al. The effects of metformin with lifestyle therapy in polycystic ovary syndrome: a randomized double-blind study. *Fertility & Sterility* 2011;**95**(3):1059–66.e1-7. [PUBMED: 21193187]

Lakryc 2003 *{published data only}*
Lakryc EM, Motta EL, Soares JM Jr, Haidar MA, de Lima GR, Baracat EC. The benefits of finasteride for hirsute women with polycystic ovary syndrome or idiopathic hirsutism. *Gynecological Endocrinology* 2003;**17**(1):57–63. [PUBMED: 12724020]

Lam 2011 *{published data only}*
Lam PM, Tam WH, Ma RC, Cheung LP, Tsui MH, Tong PC, et al. The reproductive and metabolic effect of rosiglitazone on Chinese women with polycystic ovarian syndrome--a double-blind randomized placebo-controlled study. *Fertility & Sterility* 2011;**96**(2):445–51. [PUBMED: 21722894]

Lello 2008 *{published data only}*
Colonna L, Pacifico V, Lello S, Sorge R, Raskovic D, Primavera G. Skin improvement with two different oestroprogestins in patients affected by acne and polycystic ovary syndrome: clinical and instrumental evaluation. *Journal of the European Academy of Dermatology & Venereology* 2012;**26**(11):1364–71. [PUBMED: 22011217]
* Lello S, Primavera G, Colonna L, Vittori G, Guardianelli F, Sorge R, et al. Effects of two estroprogestins containing ethynilestradiol 30 microg and drospirenone 3 mg and ethynilestradiol 30 microg and chlormadinone 2 mg on skin and hormonal hyperandrogenic manifestations. *Gynecological Endocrinology* 2008;**24**(12):718–23. [PUBMED: 19172543]

Lemay 2006 *{published data only}*
Lemay A, Dodin S, Turcot L, Déchêne F, Forest JC. Rosiglitazone and ethinyl estradiol/cyproterone acetate as single and combined treatment of overweight women with polycystic ovary syndrome and insulin resistance. *Human Reproduction* 2006;**21**(1):121–8. [PUBMED: 16199428]

Levrier 1988 *{published data only}*
Levrier M, Degrelle H, Bestaux Y, Bourry-Moreno M, Brun JP, Sailly F. Efficacy of oral contraceptives on acne. Apropos of a comparative study of Varnoline vs Diane in 69 women with acne [Efficacité sur l'acné des contraceptifs oreaux. A propos d'une étude comparative Varnoline versus Diane 35 chez 69 femmes acnéiques]. *Revue Française De Gynécologie Et D'Obstétrique* 1988;**83**(7-9):573–6. [EMBASE: 1988226069]

Lissak 1989 *{published data only}*
Lissak A, Sorokin Y, Calderon I, Dirnfeld M, Lioz H, Abramovici H. Treatment of hirsutism with cimetidine: a prospective randomized controlled trial. *Fertility & Sterility* 1989;**51**(2):247–50. [PUBMED: 2521471]

Lucas 2001 *{published data only}*
Lucas KJ. Finasteride cream in hirsutism. *Endocrine Practice* 2001;**7**(1):5–10. [PUBMED: 11250761]

Lumachi 2003 *{published data only}*
Lumachi F, Rondinone R. Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. *Fertility & Sterility* 2003;**79**(4):942–6. [PUBMED: 12749435]

Luque-Ramírez 2007 *{published data only}*
Luque-Ramírez M, Alvarez-Blasco F, Botella-Carretero JI, Martínez-Bermejo E, Lasunción MA, Escobar-Morreale HF. Comparison of ethinyl-estradiol plus cyproterone acetate versus metformin effects on classic metabolic cardiovascular risk factors in women with the polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2007;**92**(7): 2453–61. [PUBMED: 17426085]

Maciel 2004 *{published data only}*
Maciel GA, Soares Júnior JM, Alves da Motta EL, Abi Haidar M, de Lima GR, Baracat EC. Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. *Fertility & Sterility* 2004;**81**(2):355–60. [PUBMED: 14967373]

Mastorakos 2002 *{published data only}*
Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. *Fertility & Sterility* 2002;**77**(5):919–27. [PUBMED: 12009344]

Mastorakos 2006 *{published data only}*
Mastorakos G, Koliopoulos C, Deligeoroglou E, Diamanti-Kandarakis E, Creatsas G. Effects of two forms of combined oral contraceptives on carbohydrate metabolism in adolescents with polycystic ovary syndrome. *Fertility & Sterility* 2006;**85**(2):420–7. [PUBMED: 16595221]

McLellan 1989 *{published data only}*
* McLellan AR, Rentoul J, MacKie R, McInnes GT. Lack of effect of spironolactone on hair shaft diameter in hirsute females. *Postgraduate Medical Journal* 1989;**65**(765): 459–62. [PUBMED: 2690044]
McLellan AR, Rentoul J, MacKie R, McInnes GT. Spironolactone lacks efficacy in female hirsutism. *British Journal of Clinical Pharmacology* 1988;**25**(1):128P–9P.

Meyer 2007 *{published data only}*
Meyer C, McGrath BP, Teede HJ. Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. *Diabetes Care* 2007;**30**(3): 471–8. [PUBMED: 17327307]

Moghetti 2000 *{published data only}*
* Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, Perrone F, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *Journal of Clinical Endocrinology & Metabolism* 2000;**85**(1):89–94. [PUBMED: 10634370]
Negri C, Tosi F, Dorizzi R, Fortunato A, Spiazzi GG, Muggeo M, et al. Antiandrogen drugs lower serum prostate-specific antigen (PSA) levels in hirsute subjects: evidence that serum PSA is a marker of androgen action in women. *Journal of Clinical Endocrinology & Metabolism* 2000;**85**(1): 81–4. [PUBMED: 10634368]

Moghetti 2000B *{published data only}*
Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic

ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *Journal of Clinical Endocrinology & Metabolism* 2000;**85**(1):139–46. [PUBMED: 10634377]

Moltz 1984 *{published data only}*
Moltz L, Kaiser E. Medium dose oral cyproterone acetate therapy in women with moderate hyperandrogenism. *Geburtshilfe Und Frauenheilkunde* 1984;**44**(1):47–52. [EMBASE: 1984049118]

Morin-Papunen 2000 *{published data only}*
* Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *Journal of Clinical Endocrinology & Metabolism* 2000;**85**(9):3161–8. [PUBMED: 10999803]
Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2005;**152**(2):269–75. [PUBMED: 15745936]

Morin-Papunen 2003 *{published data only}*
* Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. *Journal of Clinical Endocrinology & Metabolism* 2003; **88**(1):148–56. [PUBMED: 12519844]
Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2005;**152**(2):269–75. [PUBMED: 15745936]

Müderris 2000 *{published data only}*
Müderris II, Bayram F, Güven M. A prospective, randomized trial comparing flutamide (250 mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. *Fertility & Sterility* 2000;**73**(5):984–7. [PUBMED: 10785225]

Murdoch 1987 *{published data only}*
Murdoch AP, McClean KG, Watson MJ, Dunlop W, Kendall Taylor P. Treatment of hirsutism in polycystic ovary syndrome with bromocriptine. *British Journal of Obstetrics & Gynaecology* 1987;**94**(4):358–65. [PUBMED: 3555604]

Navali 2012 *{published data only}*
Navali N, Shokoufe LA, Mallah F, Bastani P, Mashrabi O. Comparing therapeutic effects of metformin and pioglitazone in polycystic ovary syndrome (PCOS). *Pakistan Journal of Medical Sciences* 2012;**28**(3):390–4.

O'Brien 1991 *{published data only}*
O'Brien RC, Cooper ME, Murray RM, Seeman E, Thomas AK, Jerums G. Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1991;**72**(5):1008–13. [PUBMED: 1827125]

Onalan 2005 *{published data only}*
Önalan G, Goktolga U, Ceyhan T, Bagis T, Onalan R, Pabuçcu R. Predictive value of glucose-insulin ratio in PCOS and profile of women who will benefit from metformin therapy: obese, lean, hyper or normoinsulinemic?. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 2005;**123**(2):204–11. [PUBMED: 16316811]

Oner 2011 *{published data only}*
Oner G, Muderris II. A prospective randomized trial comparing low-dose ethinyl estradiol and drospirenone 24/4 combined oral contraceptive vs. ethinyl estradiol and drospirenone 21/7 combined oral contraceptive in the treatment of hirsutism. *Contraception* 2011;**84**(5):508–11. [PUBMED: 22018126]

Oner 2011B *{published data only}*
Oner G, Muderris II. Clinical, endocrine and metabolic effects of metformin vs N-acetyl-cysteine in women with polycystic ovary syndrome. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 2011;**159**(1):127–31. [PUBMED: 21831508]

Ortega-González 2005 *{published data only}*
* Ortega-González C, Cardoza L, Coutiño B, Hidalgo R, Arteaga-Troncoso G, Parra A. Insulin sensitizing drugs increase the endogenous dopaminergic tone in obese insulin-resistant women with polycystic ovary syndrome. *Journal of Endocrinology* 2005;**184**(1):233–9. [PUBMED: 15642799]
Ortega-González C, Luna S, Hernández L, Crespo G, Aguayo P, Arteaga-Troncoso G, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2005;**90**(3):1360–5. [PUBMED: 15598674]

Otta 2010 *{published data only}*
Otta CF, Wior M, Iraci GS, Kaplan R, Torres D, Gaido MI, et al. Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. *Gynecological Endocrinology* 2010;**26**(3):173–8. [PUBMED: 20148739]

Paoletti 1999 *{published data only}*
Paoletti AM, Cagnacci A, Orrù M, Ajossa S, Guerriero S, Melis GB. Treatment with flutamide improves hyperinsulinemia in women with idiopathic hirsutism. *Fertility & Sterility* 1999;**72**(3):448–53. [PUBMED: 10519615]

Pasquali 1986 *{published data only}*
Pasquali R, Fabbri R, Venturoli S, Paradisi R, Antenucci D, Melchionda N. Effect of weight loss and antiandrogenic therapy on sex hormone blood levels and insulin resistance in obese patients with polycystic ovaries. *American Journal of Obstetrics & Gynecology* 1986;**154**(1):139–44. [PUBMED: 3511703]

Pasquali 2000 *{published data only}*

Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2000;**85**(8):2767–74. [PUBMED: 10946879]

Pazos 1999 *{published data only}*

Pazos F, Escobar-Morreale HF, Balsa J, Sancho JM, Varela C. Prospective randomized study comparing the long-acting gonadotropin-releasing hormone agonist triptorelin, flutamide, and cyproterone acetate, used in combination with an oral contraceptive, in the treatment of hirsutism. *Fertility & Sterility* 1999;**71**(1):122–8. [PUBMED: 9935128]

Penna 2005 *{published data only}*

Penna IA, Canella PR, Reis RM, Silva de Sá MF, Ferriani RA. Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study. *Human Reproduction* 2005;**20**(9):2396–401. [PUBMED: 16006454]

Porcile 1991 *{published data only}*

Porcile A, Gallardo E. Long-term treatment of hirsutism: desogestrel compared with cyproterone acetate in oral contraceptives. *Fertility & Sterility* 1991;**55**(5):877–81. [PUBMED: 1827074]

Porcile 1991B *{published data only}*

Porcile A, Gallardo E. Oral contraceptive containing desogestrel in the maintenance of the remission of hirsutism: monthly versus bimonthly treatment. *Contraception* 1991; **44**(5):533–40. [PUBMED: 1839144]

Prezelj 1989 *{published data only}*

Prezelj J, Kocijancic A, Andolsek L. Dexamethasone and spironolactone in the treatment of non-tumorous hyperandrogenism. *Gynecological Endocrinology* 1989;**3**(4): 281–8. [PUBMED: 2516705]

Rautio 2005 *{published data only}*

Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2005;**152**(2):269–75. [PUBMED: 15745936]

Rittmaster 1988 *{published data only}*

Rittmaster RS, Givner ML. Effect of daily and alternate day low dose prednisone on serum cortisol and adrenal androgens in hirsute women. *Journal of Clinical Endocrinology & Metabolism* 1988;**67**(2):400–3. [PUBMED: 2969002]

Rittmaster 1990 *{published data only}*

Rittmaster RS, Thompson DL. Effect of leuprolide and dexamethasone on hair growth and hormone levels in hirsute women: the relative importance of the ovary and the adrenal in the pathogenesis of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1990;**70**(4):1096–102. [PUBMED: 2156885]

Roth 2012 *{published data only}*

Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *New England Journal of Medicine* 2007;**356**(6):551–66. [PUBMED: 17287476]

* Roth LW, Huang H, Legro RS, Diamond MP, Coutifaris C, Carson SA, et al. Altering hirsutism through ovulation induction in women with polycystic ovary syndrome. *Obstetrics & Gynecology* 2012;**119**(6):1151–6. [PUBMED: 22617579]

Schlaff D, Legro RS, Diamond MP, Coutifaris C, Zhang H. Ovulation induction with clomiphene, metformin, or a combination of the two does not affect hirsutism score over a standard course of treatment in women with polycystic ovary syndrome. *Fertility & Sterility* 2010;**94**(4 Suppl 1): S192–3. [EMBASE: 70267683]

Sabuncu 2003 *{published data only}*

Sabuncu T, Harma M, Harma M, Nazligul Y, Kilic F. Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. *Fertility & Sterility* 2003;**80**(5):1199–204. [PUBMED: 14607575]

Saeed 1993 *{published data only}*

Saeed R, Akram J, Changezi HU, Saeed M. Treatment of hirsutism in polycystic ovarian syndrome with Diane, 50 mcg ethinyl estradiol and 2 mg cyproterone acetate. *SPECIALIST/Pakistan Journal of Medical Sciences* 1993;**9** (2):109–12.

Sahin 1998 *{published data only}*

Sahin Y, Bayram F, Kelestimur F, Muderris I. Comparison of cyproterone acetate plus ethinyl estradiol and finasteride in the treatment of hirsutism. *Journal of Endocrinological Investigation* 1998;**21**(6):248–52. [EMBASE: 1998278320]

Sanam 2011 *{published data only}*

Sanam M, Ziba O. Desogestrel+ethinylestradiol versus levonorgestrel+ethinylestradiol. Which one has better affect on acne, hirsutism, and weight change. *Saudi Medical Journal* 2011;**32**(1):23–6. [EMBASE: 2011113079]

Sathyapalan 2012 *{published data only}*

Sathyapalan T, Smith KA, Coady AM, Kilpatrick ES, Atkin SL. Atorvastatin therapy decreases androstenedione and dehydroepiandrosterone sulphate concentrations in patients with polycystic ovary syndrome: randomized controlled study. *Annals of Clinical Biochemistry* 2012;**49**(Pt 1):80–5. [PUBMED: 21972424]

Schmidt 1987 *{published data only}*

Schmidt JB, Huber J, Spona J. Parenteral and oral cyproterone acetate treatment in severe hirsutism. *Gynecologic & Obstetric Investigation* 1987;**24**(2):125–30. [PUBMED: 3653783]

Smith 2006 *{published data only}*

Smith SR, Piacquadio DJ, Beger B, Littler C. Eflornithine cream combined with laser therapy in the management of

unwanted facial hair growth in women: a randomized trial. *Dermatologic Surgery* 2006;**32**(10):1237–43. [PUBMED: 17034372]

Sobbrio 1990 *{published data only}*
Sobbrio GA, Granata A, D'Arrigo F, Arena D, Panacea A, Trimarchi F, et al. Treatment of hirsutism related to micropolycystic ovary syndrome (MPCO) with two low-dose oestrogen oral contraceptives: a comparative randomized evaluation. *Acta Europaea Fertilitatis* 1990;**21**(3):139–41. [PUBMED: 2149912]

Spritzer 2000 *{published data only}*
Spritzer PM, Lisboa KO, Mattiello S, Lhullier F. Spironolactone as a single agent for long-term therapy of hirsute patients. *Clinical Endocrinology* 2000;**52**(5):587–94. [PUBMED: 10792338]

Spuy 1995 *{published data only}*
Spuy Z, Nugent F. The management of hirsutism in PCOS using GnRH agonist analogue therapy. 27th British Congress of Obstetrics and Gynaecology. 1995:242.

Stener-Victorin 2009 *{published data only}*
Stener-Victorin E, Jedel E, Janson PO, Sverrisdottir YB. Low-frequency electroacupuncture and physical exercise decrease high muscle sympathetic nerve activity in polycystic ovary syndrome. *American Journal of Physiology. Regulatory, Integrative & Comparative Physiology* 2009;**297**(2):R387–95. [PUBMED: 19494176]

Taheripanah 2010 *{published data only}*
Taheripanah R, Sepahvandi M, Entezari A, Amiri Z, Neisani Samani E. Evaluation of serum PSA after cyproterone compound treatment compared with oral contraceptive pill in hirsute polycystic ovary syndrome patients. *Middle East Fertility Society Journal* 2010;**15**(3):159–62. [EMBASE: 2010600780]

Tartagni 2000 *{published data only}*
Tartagni M, Schonauer LM, De Salvia MA, Cicinelli E, De Pergola G, D'Addario V. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertility & Sterility* 2000;**73**(4):718–23. [PUBMED: 10731531]

Tartagni 2004 *{published data only}*
Tartagni M, Schonauer MM, Cicinelli E, Petruzzelli F, De Pergola G, De Salvia MA, et al. Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women. *Fertility & Sterility* 2004;**82**(3):752–5. [PUBMED: 15374729]

Tiitinen 1994 *{published data only}*
Tiitinen A, Simberg N, Stenman UH, Ylikorkala O. Estrogen replacement does not potentiate gonadotropin-releasing hormone agonist-induced androgen suppression in treatment of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1994;**79**(2):447–51. [PUBMED: 8045961]

Unfer 2000 *{published data only}*
Unfer V, Gerli S, Costabile L, Renzo G. A prospective, randomized study comparing ethinylestradiol plus ciproterone acetate and flutamide in the treatment of hirsutism in PCOS patients. *Gynecological Endocrinology* 2000;**14**(Suppl 2):36.

van Vloten 2002 *{published data only}*
van Vloten WA, van Haselen CW, van Zuuren EJ, Gerlinger C, Heithecker R. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. *Cutis* 2002;**69**(Suppl 4):2–15. [PUBMED: 12096825]

Vegetti 1996 *{published data only}*
Vegetti W, Testa G, Maggioni P, Motta T, Falsetti L, Crosignani PG. An open randomized comparative study of an oral contraceptive containing ethinyl estradiol and cyproterone acetate. *Gynecologic & Obstetric Investigation* 1996;**41**(4):260–8. [PUBMED: 8793497]

Venturoli 1998 *{published data only}*
Venturoli S, Ravaioli B, Bagnoli A, Colombo FM, Macrelli S, Iadarola I, et al. Contraceptive and therapeutic effectiveness of two low-dose ethinylestradiol and cyproterone acetate regimens in the treatment of hirsute patients. *European Journal of Contraception & Reproductive Health Care* 1998;**3**(1):29–33. [PUBMED: 9678070]

Venturoli 1999 *{published data only}*
* Venturoli S, Marescalchi O, Colombo FM, Macrelli S, Ravaioli B, Bagnoli A, et al. A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1999;**84**(4):1304–10. [PUBMED: 10199771]
Venturoli S, Vianello F, Bagnoli A, Colombo FM, Ravaioli B, Macrelli S. Comparison of ciproterone acetate, finasteride, flutamide and ketoconazole in the treatment of hirsutism. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167 Suppl):71.

Vermeulen 1988 *{published data only}*
Vermeulen A, Rubens R. Effects of cyproterone acetate plus ethinylestradiol low dose on plasma androgens and lipids in mildly hirsute or acneic young women. *Contraception* 1988;**38**(4):419–28. [PUBMED: 2974791]

Vexiau 1995 *{published data only}*
Vexiau P, Fiet J, Conard J, Abramovici Y, Boudou P, Hardy N, et al. 17 beta-estradiol: oral or parenteral administration in hyperandrogenic women? Metabolic tolerance in association with cyproterone acetate. *Fertility & Sterility* 1995;**63**(3):508–15. [PUBMED: 7851579]

Vigorito 2007 *{published data only}*
Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* 2007;**92**(4):1379–84. [PUBMED: 17264174]

Visnovský 2010 *{published data only}*
Visnovský J, Biringer K, Svecová I, Biringerová Z. Hormonal treatment effectivity in hyperandrogenic syndrome [Efect

hormonálnej liečbe hyperandrogénneho syndrómu]. *Ceska Gynekologie* 2010;**75**(5):481–5. [PUBMED: 21374929]

Wang 2012 *{published data only}*

Wang QY, Huang W, Song YS, Li X, Shen LL. The impact of oral contraceptives, metformin and lifestyle modification on the metabolism disorder in polycystic ovary syndrome women: A randomized controlled trial. *International Journal of Gynecology & Obstetrics* 2012;**119**(Suppl 3):S482. [EMBASE: 70905961]

Wolf 2007 *{published data only}*

Jouanique C. Eflornithine: evidence of efficacy [L'éflornithin: les preuves de son efficacité]. *Annales de Dermatologie et de Venereologie* 2005;**132**(6-7 Pt 2):3S11–3. [PUBMED: 16223125]

Mathes BM, Manna V, Huber FJ, Jackson JD, Bogaerts J, Schrode KBA. Novel approach to treating excessive facial hair in women. Results of safety and efficacy studies with eflornithine hydrochloride 13.9% cream. *Journal of Investigative Dermatology* 2003;**8**(1):126.

* Wolf JE, Shander D, Huber F, Jackson J, Lin CS, Mathes BM, et al. Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. *International Journal of Dermatology* 2007;**46**(1):94–8. [PUBMED: 17214730]

Wong 1995 *{published data only}*

Wong IL, Morris RS, Chang L, Spahn MA, Stanczyk FZ, Lobo RA. A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women. *Journal of Clinical Endocrinology & Metabolism* 1995;**80**(1):233–8. [PUBMED: 7829618]

Zheng 2005 *{published data only}*

Zheng J, Cao Z, Zong L. Effect of rosiglitazone and metformin on clomiphene citrate resistance in women with polycystic ovary syndrome. *Academic Journal of Xi'an Jiaotong University* 2005;**17**(1):62-5 +71. [EMBASE: 2005222450]

References to studies excluded from this review

Acién 1997 *{published data only}*

Acién P, Mauri M, Gutierrez M. Clinical and hormonal effects of the combination gonadotrophin-releasing hormone agonist plus oral contraceptive pills containing ethinyl-oestradiol (EE) and cyproterone acetate (CPA) versus the EE-CPA pill alone on polycystic ovarian disease-related hyperandrogenisms. *Human Reproduction* 1997;**12**(3):423–9. [PUBMED: 9130733]

Anderson 1977 *{published data only}*

Anderson JAR, Browning MCK. An assessment of (1) cyproterone acetate and (2) ethinyloestradiol and lynoestrenol (Minilyn) in the treatment of 'idiopathic' hirsutism. *British Journal of Dermatology* 1977;**97**(15):20–1. [EMBASE: 0978137436]

Ansarin 2007 *{published data only}*

Ansarin H, Mehregan R, Hosseini J. Comparison of spironolactone plus cyproterone acetate plus cyproterone compound with spironolactone plus cyproterone compound in hirsutism: a randomized clinical trial. *Iranian Journal of Dermatology* 2004;**7**(3):156–65.

Avnstorp 1982 *{published data only}*

Avnstorp C, Hamann K. Epilation of facial hirsutism in women. A study of the therapeutic effects. *Ugeskrift for Laeger* 1982;**144**(5):315–7. [PUBMED: 7041385]

Baranowska 1983 *{published data only}*

Baranowska B, Stopinska-Gluszak U, Niewiadomska A, Rozbicka G. Analysis of the results of treatment of idiopathic hirsutism and hirsutism in patients with polycystic ovary syndrome with androcur (cyproterone acetate) [Analiza wynikow leczenia Androcurem (octanem cyproteronu) hirsutyzmu idiopatycznego i hirsutyzmu u pacjentek z zespollem policystycznych jajnikow]. *Endokrynologia Polska* 1983;**34**(4):227–34. [EMBASE: 6228420]

Barrett-Connor 1999 *{published data only}*

Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, et al. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. *Journal of Reproductive Medicine* 1999;**44**(12):1012–20. [PUBMED: 10649811]

Barth 1989 *{published data only}*

Barth JH, Cherry CA, Wojnarowska FT, Dawber RPR. Cyproterone acetate in the treatment of hirsute women. *British Journal of Dermatology* 1989;**121**(Suppl 34):31.

Batukan 2006 *{published data only}*

Batukan C, Muderris II. Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism. *Fertility & Sterility* 2006;**85**(2):436–40. [PUBMED: 16595223]

Bazex 1982 *{published data only}*

Bazex J, Boubes A, Aschieri M. Clinical trial of oestro-anti-androgenic in the treatment of the cutaneous manifestations of hyperandrogenies [Essai clinique d'une association oestro–anti–androgenique dans le traitement des manifestations cutanees des hyperandrogenies]. *Revue de Medecine de Toulouse* 1982;**18**(6 Suppl):399–401. [EMBASE: 1982194518]

Benjamin 1971 *{published data only}*

Benjamin F, Kolodny HD, Schwartz ED. The comparative effects of the administration of cortisone, estrogen-progestin, and placebo on the clinical manifestations of the polycystic ovary (Stein-Leventhal) syndrome. *Journal of Reproductive Medicine* 1971;**6**(6):266–9. [PUBMED: 4255649]

Bridger 2006 *{published data only}*

Bridger T, MacDonald S, Baltzer F, Rodd C. Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome. *Archives of Pediatrics & Adolescent Medicine* 2006;**160**(3):241–6. [EMBASE: 2006120339]

Buckshee 1986 *{published data only}*

Buckshee K, Ahuja MM. Therapeutic evaluation of spironolactone in Indian women with hirsutism. *Journal*

of the Association of Physicians of India 1986;**34**(8):577–9. [PUBMED: 3793679]

Carmina 1997 ***{published data only}***
Carmina E, Lobo RA. Gonadotrophin-releasing hormone agonist therapy for hirsutism is as effective as high dose cyproterone acetate but results in a longer remission. *Human Reproduction* 1997;**12**(4):663–6. [PUBMED: 9159420]

Castel-Branco 1998 ***{published data only}***
* Castelo-Branco C, Martínez de Osaba MJ, Pons F, Vanrell JA. Effects on bone mass of two oral contraceptives containing ethinylestradiol and cyproterone acetate or desogestrel: results of a 2-year follow-up. *European Journal of Contraception & Reproductive Health Care* 1998;**3**(2): 79–84. [PUBMED: 9710711]
Fortuny A, Castelo Branco C, Martinez de Osaba MJ, Pons F. Gonadotrophin-releasing hormone analogue plus contraceptives in women with severe hirsutism: effects on hair, bone and hormones after one-year. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(Suppl):76.

Castello 1991 ***{published data only}***
Castello R, Moghetti A, Magnani C, Zardini G, Furlani L, Tosi F, et al. Spironolactone versus spironolactone plus liquorice in hirsutism: hormonal evaluation. *Journal of Gynaecological Endocrinology* 1991;**7-8**(1-4):34–7. [EMBASE: 1993278155]

Codner 2009 ***{published data only}***
Codner E, Iñiguez G, López P, Eyzaguirre F, Assenjo S, Torrealba I, et al. Metformin for the treatment of hyperandrogenism in adolescents with type 1 diabetes mellitus: a double blind randomized study. *Hormone Research* 2009;**72**(Suppl 3):431.

Cremoncini 1976 ***{published data only}***
Cremoncini C, Vignati E, Libroia A. Treatment of hirsutism and acne in women with two combinations of cyproterone acetate and ethinylestradiol. *Acta Europaea Fertilitatis* 1976; **7**(4):299–314. [PUBMED: 140576]

Cullberg 1985 ***{published data only}***
Cullberg G, Hamberger L, Mattsson LA, Mobacken H, Samsioe G. Effects of a low-dose desogestrel-ethinylestradiol combination on hirsutism, androgens and sex hormone binding globulin in women with a polycystic ovary syndrome. *Acta Obstetricia et Gynecologica Scandinavica* 1985;**64**(3):195–202. [PUBMED: 3160211]

Cunliffe 1973 ***{published data only}***
Cunliffe WJ, Williams M. Topical aminoglutethimide in hirsutism. *British Journal of Dermatology* 1973;**88**(1):95–6. [PUBMED: 4568661]

Dahlgren 1998 ***{published data only}***
Dahlgren E, Landin K, Krotkiewski M, Holm G, Janson PO. Effects of two antiandrogen treatments on hirsutism and insulin sensitivity in women with polycystic ovary syndrome. *Human Reproduction* 1998;**13**(10):2706–11. [PUBMED: 9804218]

Dennerstein 1984 ***{published data only}***
Dennerstein L, Callan A, Warne G, Montalto J, Brown J, Burrows G, et al. The effects of benzodiazepines on hormones in women with idiopathic hirsutism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 1984;**8** (1):11–7. [PUBMED: 6145182]

Devoto 2000 ***{published data only}***
Devoto E, Aravena L, Ríos R. Treatment of hirsutism with spironolactone and with spironolactone plus dexamethasone [Tratamiento del hirsutismo con espironolactona y con espironolactona más dexametasona]. *Revista Médica de Chile* 2000;**128**(8):868–75. [EMBASE: 11129548]

Devoto 2004 ***{published data only}***
Devoto CE, Aravena CL. Effectiveness of flutamide alone or combined with oral contraceptives in the treatment of hirsutism in women [Eficacia de la flutamida en eltratamiento del hirsutismo. Contribución del uso combinadocon anticonceptivos orales en mujeres normoandrogénicas]. *Revista Médica de Chile* 2004;**132**(7): 845–52. [EMBASE: 15379332]

Dikensoy 2009 ***{published data only}***
Dikensoy E, Balat O, Pence S, Akcali C, Cicek H. The risk of hepatotoxicity during long-term and low-dose flutamide treatment in hirsutism. *Archives of Gynecology & Obstetrics* 2009;**279**(3):321–7. [PUBMED: 18607612]

Erdmann 1994 ***{published data only}***
Erdmann D, Schindler EM, Schindler AE. Ovarian suppression with Diane 35/50 [Die Ovarielle Suppression Unter Diane 35/50]. *Geburtshilfe und Frauenheilkunde* 1994;**54**(11):627–33. [EMBASE: 1994361652]

Erenus 1995 ***{published data only}***
Erenus M. Efficacy of flutamide versus spironolactone. *Fertility & Sterility* 1995;**63**(3):680. [PUBMED: 7851609]

Escobar-Morreale 1998 ***{published data only}***
Escobar-Morreale HF, Serrano-Gotarredona J, García-Robles R, Varela C, Sancho JM. Abnormalities in the serum insulin-like growth factor-1 axis in women with hyperandrogenism. *Fertility & Sterility* 1998;**70**(6): 1090–100. [PUBMED: 9848301]

Falsetti 1997 ***{published data only}***
Falsetti L, De Fusco D, Eleftheriou G, Rosina B. Treatment of hirsutism by finasteride and flutamide in women with polycystic ovary syndrome. *Gynecological Endocrinology* 1997;**11**(4):251–7. [PUBMED: 9272421]

Falsetti 1997B ***{published data only}***
* Falsetti L, De FD, Rosina B. The use of finasteride and flutamide in the management of hirsutism [Finasteride e flutamide nel trattamento dell'irsutismo]. *Minerva Ginecologica* 1997;**49**(10):463–8. [EMBASE: 1997372999]
Falsetti L, Scalchi S, Bugari G. Nonsteroidal antiandrogens in the treatment of hirsutism [Gli antiandrogeni non steroidei nel trattamento dell'irsutismo]. *Giornale Italiano di Ostetricia E Ginecologia* 1998;**20**(10):459–63. [EMBASE: 1998395459]

Fruzzetti 1993 *{published data only}*
Fruzzetti F, De Lorenzo D, Ricci C, Fioretti P. Clinical and endocrine effects of flutamide in hyperandrogenic women. *Fertility & Sterility* 1993;**60**(5):806–13. [PUBMED: 8224265]

Givens 1976 *{published data only}*
Givens JR, Andersen RN, Wiser WL, Umstot ES, Fish SA. The effectiveness of two oral contraceptives in suppressing plasma androstenedione, testosterone, LH, and FSH, and in stimulating plasma testosterone-binding capacity in hirsute women. *American Journal of Obstetrics & Gynecology* 1976; **124**(4):333–9. [PUBMED: 1251854]

Gökmen 1996 *{published data only}*
Gökmen O, Senöz S, Gülekli B, Iik AZ. Comparison of four different treatment regimes in hirsutism related to polycystic ovary syndrome. *Gynecological Endocrinology* 1996;**10**(4):249–55. [PUBMED: 8908525]

Gomez 1987 *{published data only}*
Gomez F, Ramelet AA, Rüedi B, Mühlemann M. Lack of effect of a spironolactone-containing cream on hair growth in hirsute women. *Dermatologica* 1987;**174**(2):102–3. [PUBMED: 3556697]

Gregoriou 2000 *{published data only}*
Gregoriou O, Bakas P, Konidaris S, Papadias K, Mathiopoulos D, Creatsas G. The effect of combined oral contraception with or without spironolactone on bone mineral density of hyperandrogenic women. *Gynecological Endocrinology* 2000;**14**(5):369–73. [PUBMED: 11109976]

Grigoriou 1996 *{published data only}*
Grigoriou O, Papadias C, Konidaris S, Antoniou G, Karakitsos P, Giannikos L. Comparison of flutamide and cyproterone acetate in the treatment of hirsutism: a randomized controlled trial. *Gynecological Endocrinology* 1996;**10**(2):119–23. [PUBMED: 8701785]

Grund 1975 *{published data only}*
Grund E, Schmidt-Elmendorff H. The treatment of virilizing syndromes. Comparative clinical studies of 2 antiandrogen-active gestagens (cyproterone acetate, megestrol acetate [Behandlung von Virilisierungserscheinungen: Vergleichende klinische Untersuchung zweier antiandrogenwirksamer Gestagene (Cyproteronazetat, Megestrolazetat]. *Die Medizinische Welt* 1975;**26**(48):2180–7. [PUBMED: 128684]

Gupta 1978 *{published data only}*
Gupta R, Buckshee K, Baliga N, Hingorani V. Evaluation of estrogen-progesterone and dexamethasone therapy in hirsutism. *Journal of Steroid Biochemistry* 1978;**9**(9):849. [MEDLINE: 0979025198]

Guzick 1994 *{published data only}*
Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertility & Sterility* 1994;**61**(4):598–604. [PUBMED: 8150098]

Hahn 2004 *{published data only}*
Hahn S, Quadbeck B, Elsenbruch S, Gärtner R, Finke R, Mann K, et al. Metformin, an efficacious drug in the treatment of polycystic ovary syndrome [Metformin - ein effektiver Therapieansatz in der Behandlung des Polyzystischen Ovarsyndroms]. *Deutsche Medizinische Wochenschrift* 2004;**129**(19):1059–64. [EMBASE: 2004264208]

Inal 2005 *{published data only}*
Inal MM, Yildirim Y, Taner CE. Comparison of the clinical efficacy of flutamide and spironolactone plus Diane 35 in the treatment of idiopathic hirsutism: a randomized controlled study. *Fertility & Sterility* 2005;**84**(6):1693–7. [PUBMED: 16359967]

Jasonni 1991 *{published data only}*
Jasonni VM, Bulletti C, Naldi S, Di Cosmo E, Cappuccini F, Flamigni C. Treatment of hirsutism by an association of oral cyproterone acetate and transdermal 17 beta-estradiol. *Fertility & Sterility* 1991;**55**(4):742–5. [PUBMED: 1826278]

Karakurt 2008 *{published data only}*
Karakurt F, Sahin I, Güler S, Demirbas B, Culha C, Serter R, et al. Comparison of the clinical efficacy of flutamide and spironolactone plus ethinyloestradiol/cyproterone acetate in the treatment of hirsutism: a randomised controlled study. *Advances in Therapy* 2008;**25**(4):321–8. [PUBMED: 18389188]

Kazerooni 2010 *{published data only}*
Kazerooni T, Shojaei-Baghini A, Dehbashi S, Asadi N, Ghaffarpasand F, Kazerooni Y. Effects of metformin plus simvastatin on polycystic ovary syndrome: a prospective, randomized, double-blind, placebo-controlled study. *Fertility & Sterility* 2010;**94**(6):2208–13. [PUBMED: 20079899]

Keletimur 1998 *{published data only}*
Keletimur F, Sahin Y. Comparison of Diane 35 and Diane 35 plus spironolactone in the treatment of hirsutism. *Fertility & Sterility* 1998;**69**(1):66–9. [PUBMED: 9457935]

Keletimur 2004 *{published data only}*
Keletimur F, Everest H, Unlühizarci K, Bayram F, Sahin Y. A comparison between spironolactone and spironolactone plus finasteride in the treatment of hirsutism. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2004;**150**(3):351–4. [PUBMED: 15012621]

Knopp 2001 *{published data only}*
Knopp RH, Broyles FE, Cheung M, Moore K, Marcovina S, Chandler WL. Comparison of the lipoprotein, carbohydrate, and hemostatic effects of phasic oral contraceptives containing desogestrel or levonorgestrel. *Contraception* 2001;**63**(1):1–11. [PUBMED: 11257242]

Lachnit-Fixson 1979 *{published data only}*
Lachnit-Fixson U. The development and evaluation of an ovulation inhibitor (Diane) containing an antiandrogen. *Acta Obstetricia et Gynecologica Scandinavica* 1979;**58**(Suppl 88):33–42. [EMBASE: 1980079147]

Landman 2001 *{published data only}*
Landman RE, Jacobs TP, Azziz R, Ehrmann D, Legro RS, Whitcomb R, et al. Troglitazone use in polycystic ovary

syndrome. *Journal of Clinical Endocrinology & Metabolism* 2001;**86**(10):5090–1. [EMBASE: 2001384970]

Le Donne 2012 ***{published data only}***

Le Donne M, Alibrandi A, Giarrusso R, Lo Monaco I, Muraca U. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition [Dieta, Metformina e Inositolo in Donne Sovrappeso e Obese Con Sindrome Dell'Ovaio Policistico: Effetti Sulla Composizione Corporea]. *Minerva Ginecologica* 2012;**64**(1):23–9. [EMBASE: 2012236009]

Lee 2000 ***{published data only}***

Lee O, Farquhar C, Toomath R, Jepson R. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne [Spironolacton versus Placebo oder in Kombination mit Steroiden bei Hirsutismus und/oder Acne]. *Schweizerische Rundschau Fur Medizin Praxis* 2000; **89**(21):924. [EMBASE: 2000181606]

Lobo 1985 ***{published data only}***

Lobo RA, Shoupe D, Serafini P, Brinton D, Horton R. The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. *Fertility & Sterility* 1985;**43**(2):200–5. [PUBMED: 3967781]

Lunde 1987 ***{published data only}***

Lunde O, Djøseland O. A comparative study of Aldactone and Diane in the treatment of hirsutism. *Journal of Steroid Biochemistry* 1987;**28**(2):161–5. [PUBMED: 3626553]

Madani 2012 ***{published data only}***

Madani T, Irani S, Ashrafi M, Nabavi M.A. The effect of flutamide on ovulation induction in PCOS patients. *International Journal of Fertility and Sterility* 2012;**6**(1): 65–70.

Manieri 1997 ***{published data only}***

Manieri C, Grosso T, Bisceglie C, Fornengo R, Tagliabue M, Martin V. Finasteride in idiopathic hirsutism. *International Journal of Immunopathology & Pharmacology* 1997;**10**(2): 139–45. [PUBMED: 1997237614]

Medical Letter 2000 ***{published data only}***

No authors listed. Eflornithine cream for facial hair reduction. *Medical Letter on Drugs and Therapeutics* 2000; **42**(1089):96. [EMBASE: 2000368491]

Mowbray 1959 ***{published data only}***

Mowbray RR, Spence AW, Medvei VC, Robinsom AM. Steroid therapy in hirsutism and virilism. *British Medical Journal* 1959;**2**(5150):456–9. [PUBMED: 14424812]

Müderris 1997 ***{published data only}***

Müderris II, Bayram F, Sahin Y, Keletimur F. A comparison between two doses of flutamide (250 mg/d and 500 mg/d) in the treatment of hirsutism. *Fertility & Sterility* 1997;**68** (4):644–7. [PUBMED: 9341603]

Nielsen 1985 ***{published data only}***

Nielsen DR, Larsen J, Pedersen IM, Starup J. Influence on androgens in the serum and urine and on urinary cortisol [Hirsutisme behandlet med cyproteronacetat og etinylostradiol. Indvirkningen pa androgener i serum og urin samt pa urin–kortisol]. *Ugeskrift for Laeger* 1985;**147** (33):2589–93. [PUBMED: 2933857]

Paggi 1981 ***{published data only}***

Paggi A, Leri DO, Parrettini S. A short clinical trial of cyproterone acetate in the treatment of idiopathic hirsutism [Sperimentazione Clinica Breve Con Ciproterone Acetato Nella Terapia Degli Irsutismi Idiopatici]. *Clinica Terapeutica* 1981;**96**(4):443–53. [EMBASE: 1982104209]

Pai 1982 ***{published data only}***

Pai IF, Wu YC, Lu YC. Clinical trial of cyproterone acetate-ethinyl oestradiol compound on androgen dependent skin disorders. *Taiwan i Hsueh Hui Tsa Chih Journal of the Formosan Medical Association* 1982;**81**(8):1048–55. [PUBMED: 6217284]

Pedersen 1985 ***{published data only}***

Pedersen IM, Nielsen DR, Larsen J, Starup J. Hirsutism treated with cyproterone acetate and ethinyl estradiol. Evaluation of the clinical effect [Hirsutisme Behandlet Med Cyproteronacetat of Etinylostradiol. Vurdering Af Den Kliniske Effekt]. *Ugeskrift for Laeger* 1985;**147**(33):2594–6. [PUBMED: 2933858]

Peereboom-Wynia 1985 ***{published data only}***

Peereboom-Wynia JD, Stolz E, van Joost T, Kleiman H. A comparative study of the effects of electrical epilation of beard hairs in women with hirsutism by diathermy and by the blend method. *Archives of Dermatological Research* 1985; **278**(1):84–6. [PUBMED: 4096535]

Pugeat 1991 ***{published data only}***

Pugeat M, Nicolas MH, Dechaud H, Elmidani M. Administration of cyproterone acetate and natural oestrogens in the treatment of hirsutism [Association d'acétate de cyprotérone et d'estrogènes naturels dans le traitement de l'hirsutisme]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 1991;**20**(8): 1057–62. [EMBASE: 1992119062]

Rubens 1985 ***{published data only}***

Ruben R, Vermeulen A. Antiandrogens in the treatment of hirsutism. *Journal of Steroid Biochemistry* 1985;**23**(Suppl): 33S.

Sahin 2001 ***{published data only}***

Sahin Y, Dilber S, Keletimur F. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertility & Sterility* 2001;**75**(3):496–500. [PUBMED: 11239530]

Sert 2003 ***{published data only}***

Sert M, Tetiker T, Kirim S. Comparison of the efficiency of anti-androgenic regimens consisting of spironolactone, Diane 35, and cyproterone acetate in hirsutism. *Acta Medica Okayama* 2003;**57**(2):73–6. [PUBMED: 12866746]

Siegberg 1987 ***{published data only}***

Siegberg R, Ylöstalo P, Laatikainen T, Pelkonen R, Stenman UH. Endocrine and clinical effects of spironolactone in female hyperandrogenism. *Archives of Gynecology* 1987;**240** (2):125–30. [PUBMED: 3566358]

Taner 2002 ***{published data only}***

Taner C, Inal M, Baogul O, Onoglu A, Karanfil C, Tinar S, et al. Comparison of the clinical efficacy and safety of flutamide versus flutamide plus an oral contraceptive in the

treatment of hirsutism. *Gynecologic & Obstetric Investigation* 2002;**54**(2):105–8. [PUBMED: 12566753]

Thomas 1985 *{published data only}*
Thomas AK, Slobodniuk R, Taft J, Cooper M, Montalto J, Jerums G. The treatment of hirsutism: experience with cyproterone acetate and spironolactone. *Australasian Journal of Dermatology* 1985;**26**(1):19–24. [PUBMED: 2933024]

Tolino 1996 *{published data only}*
Tolino A, Petrone A, Sarnacchiaro F, Cirillo D, Ronsini S, Lombardi G, et al. Finasteride in the treatment of hirsutism: new therapeutic perspectives. *Fertility & Sterility* 1996;**66**(1):61–5. [PUBMED: 8752612]

Unlühizarci 2002 *{published data only}*
Unlühizarci K K, Everest H, Bayram F, Keletimur F. Comparison of spironolactone and spironolactone plus finasteride in the treatment of hirsutism. *Fertility & Sterility* 2002;**78**(6):1331–3. [PUBMED: 12477537]

Unluhizarci 2009 *{published data only}*
Unluhizarci K, Ozel D, Tanriverdi F, Karaca Z, Kelestimur F. A comparison between finasteride, flutamide, and finasteride plus flutamide combination in the treatment of hirsutism. *Journal of Endocrinological Investigation* 2009;**32**(1):37–40. [PUBMED: 19337013]

van Wayjen 1976 *{published data only}*
van Wayjen RG, van den Ende A. Anti-androgenic steroid cyproterone acetate. Clinical pharmacology and therapeutic use in hirsutism and acne [Het anti–androgene steroid cyproteron–acetaat. Klinische farmacologie en toepassing bij hirsutisme en acne]. *Nederlands Tijdschrift Voor Geneeskunde* 1976;**120**(5):189–95. [PUBMED: 129710]

Vicente 2009 *{published data only}*
Vicente RA, Leite e Silva VR, Baby AR, Velasco MV, Bedin V. Double-blind, randomized, placebo-controlled trial of a cream containing the Stryphnodendron adstringens (Martius) Coville bark extract for suppressing terminal hair growth. *Journal of the European Academy of Dermatology & Venereology* 2009;**23**(4):410–4. [PUBMED: 19192016]

Wagner 1993 *{published data only}*
Wagner RF Jr. Medical and technical issues in office electrolysis and thermolysis. *Journal of Dermatologic Surgery & Oncology* 1993;**19**(6):575–7. [PUBMED: 8509519]

Weiss 2007 *{published data only}*
Weiss J. Promising results of drospirenone in the treatment of hirsutism [Therapie mit Drosiperon bei Hirsutismus Erfolg versprechend]. *Geburtshilfe und Frauenheilkunde* 2007;**67**(8):806. [EMBASE: 2007499605]

Wild 1991 *{published data only}*
Wild RA, Demers LM, Applebaum-Bowden D, Lenker R. Hirsutism: metabolic effects of two commonly used oral contraceptives and spironolactone. *Contraception* 1991;**44**(2):113–24. [PUBMED: 1893706]

Yari 2010 *{published data only}*
Yari F, Ghafarzadeh M, Vahabi S, Khadish A, Yari A. Clomiphene citrate and dexamethasone in treatment of polycystic ovary syndrome and infertility in Khoramabad. *Journal Fur Reproduktionsmedizin Und Endokrinologie* 2010;**7**(4):369. [EMBASE: 70300035]

Yilmaz 2005 *{published data only}*
Yilmaz M, Karakoç A, Törüner FB, Cakir N, Tiras B, Ayvaz G, et al. The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. *Gynecological Endocrinology* 2005;**21**(3):154–60. [PUBMED: 16335907]

Yücelten 1999 *{published data only}*
Yücelten D, Erenus M, Gürbüz O, Durmuo ğ lu F. Recurrence rate of hirsutism after 3 different antiandrogen therapies. *Journal of the American Academy of Dermatology* 1999;**41**(1):64–8. [PUBMED: 10411413]

References to studies awaiting assessment

Akha 2014 *{published data only}*
Akha O, Rabiei K, Kashi Z, Bahar A, Zaeif-Khorasani E, Kosaryan M, et al. The effect of fennel (Foeniculum vulgare) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism. A randomized placebo controlled clinical trial. *Caspian Journal of Internal Medicine* 2014;**5**(1):26–9. [PUBMED: 24490010]

Atabekoglu 2013 *{published data only}*
Atabekoglu CS, Sukur YE, Kahraman K, Ozmen B, Sonmezer M, Berker B. Comparison of two oral contraceptive forms containing cyproterone acetate and drospirenone in the treatment of patients with polycystic ovary syndrome. *Fertility & Sterility* 2013;**100**(3 Suppl 1): S348. [EMBASE: 71164969]

Chung 2014 *{published data only}*
Chan SSC, Yiu AKW, Chung JPW. A randomised, cross-over study of medroxyprogesterone acetate and Diane-35 in adolescents with polycystic ovary syndrome. *BJOG: An International Journal of Obstetrics & Gynaecology* 2013;**120**: 345–6. [EMBASE: 71136407]
* Chung JP, Yiu AK, Chung TK, Chan SS. A randomized crossover study of medroxyprogesterone acetate and diane-35 in adolescent girls with polycystic ovarian syndrome. *Journal of Pediatric & Adolescent Gynecology* 2014;**27**(3): 166–71. [PUBMED: 24656700]

Ibañez 2013 *{published data only}*
Ibáñez L, Diaz M, Sebastiani G, Marcos MV, Lopez-Bermejo A, De Zegher F. Oral contraception versus insulin sensitisation for 18 months in non-obese adolescents with androgen excess: post-treatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity and menstrual regularity. *Hormone Research in Paediatrics* 2013;**80**:170. [EMBASE: 71246786]
* Ibáñez L, Díaz M, Sebastiani G, Marcos MV, López-Bermejo A, de Zegher F. Oral contraception vs insulin sensitization for 18 months in nonobese adolescents with androgen excess: posttreatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity, and menstrual regularity. *Journal of Clinical Endocrinology & Metabolism* 2013;**98**(5):E902–7. [PUBMED: 23547047]

Lai 2014 *{published data only}*
Lai L, Flower A, Moore M, Lewith G. Chinese herbal medicine and polycystic ovary syndrome: a randomized feasibility and pilot study in the United Kingdom. *Journal of Alternative & Complementary Medicine* 2014;**20**(5): A61–2. [EMBASE: 71474759]

Martin Hernandez 1995 *{published data only}*
Martin Hernandez T, Jorquera E, Torres A, Camacho F, Herrera E. Flutamide versus cyproterone acetate in the treatment of policystic ovary syndrome associated hirsutism [Comparacion de la eficacia de la flutamida y el acetato de ciproterona en el tratamiento del hirsutismo asociado al sindrome de los ovarios poliquisticos]. *Actas Dermo-Sifiliográficas* 1995;**86**(6):327–34. [EMBASE: 1995209158]

Mazza 2014 *{published data only}*
Mazza A, Fruci B, Guzzi P, D'Orrico B, Malaguarnera R, Veltri P, et al. In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone. *Nutrition, Metabolism & Cardiovascular Diseases* 2014;**24** (2):132–9. [PUBMED: 23845740]

Mirfeizi 2013 *{published data only}*
Mirfeizi M. Comparison of the effects of a diet and physical activity trial in obese women with polycystic ovary syndrome. *Journal of Diabetes* 2013;**5**:16. [EMBASE: 71034570]

Nidhi 2013 *{published data only}*
Nidhi R, Padmalatha V, Nagarathna R, Amritanshur R. Effects of a holistic yoga program on endocrine parameters in adolescents with polycystic ovarian syndrome: a randomized controlled trial. *Journal of Alternative & Complementary Medicine* 2013;**19**(2):153–60. [PUBMED: 22808940]

Romualdi 2013 *{published data only}*
Romualdi D, De Cicco S, Busacca M, Gagliano D, Lanzone A, Guido M. Clinical efficacy and metabolic impact of two different dosages of ethinyl-estradiol in association with drospirenone in normal-weight women with polycystic ovary syndrome: a randomized study. *Journal of Endocrinological Investigation* 2013;**36**(8):636–41. [PUBMED: 24105072]

Sangeeta 2012 *{published data only}*
* Sangeeta S. Metformin and pioglitazone in polycystic ovarian syndrome: a comparative study. *Journal of Obstetrics & Gynaecology of India* 2012;**62**(5):551–6. [PUBMED: 24082557]
Tagliaferri V, Busacca M, Gagliano D, Di Florio C, Tartaglia C, Cirella E, et al. Clinical efficacy and metabolic impact of two different dosages of ethinyl-estradiol in association with drospirenone in normal-weight women with polycystic ovary syndrome. *Human Reproduction* 2012;**27**(Suppl 2): Poster 545. [EMBASE: 71113752]

Tartagni 2014 *{published data only}*
Tartagni MV, Alrasheed H, Damiani GR, Montagnani M, De Salvia MA, De Pergola G, et al. Intermittent low-dose finasteride administration is effective for treatment of hirsutism in adolescent girls: a pilot study. *Journal of Pediatric & Adolescent Gynecology* 2014;**27**(3):161–5. [PUBMED: 24559619]

Tirabassi 2013 *{published data only}*
Tirabassi G, Giovannini L, Paggi F, Panin G, Panin F, Papa R, et al. Possible efficacy of lavender and tea tree oils in the treatment of young women affected by mild idiopathic hirsutism. *Journal of Endocrinological Investigation* 2013;**36** (1):50–4. [PUBMED: 23211454]

References to ongoing studies

IRCT201104251760N13 *{unpublished data only}*
IRCT201104251760N13. Comparison of combined oral contraceptive Yasmin and Cyproteron compound on hirsutism and androgens in women with a polycystic ovary syndrome. //www.irct.ir/searchresult.php?id=1760&number=13 (accessed 3 September 2014).

IRCT2013072214106N1 *{unpublished data only}*
IRCT2013072214106N1. Studying and preparing semi-solid formulations of finastride and clinical evaluation of optimal form in the treatment of hirsutism. //www.irct.ir/searchresult.php?keyword=&id=14106&number=1&prt=5156&total=10&m=1 (accessed 3 September 2014).

ISRCTN01915371 *{unpublished data only}*
ISRCTN01915371. Weight loss in obese women with polycystic ovary syndrome (PCOS). //controlled-trials.com/ISRCTN01915371 (accessed 3 September 2014).

ISRCTN29234515 *{unpublished data only}*
ISRCTN29234515. Efficacy of low-dose treatment with insulin sensitizers and antiandrogens versus that of an oral contraceptive on hirsutism, irregular menses, anovulation, body fat and markers of type 2 diabetes and cardiovascular risk in girls with androgen excess and elevated insulin levels and without pregnancy risk. //controlled-trials.com/ISRCTN29234515 (accessed 3 September 2014).

NCT00145340 *{unpublished data only}*
NCT00145340. Pioglitazone treatment in polycystic ovary syndrome. //clinicaltrials.gov/show/NCT00145340 (accessed 3 September 2014).

NCT00152048 *{unpublished data only}*
NCT00152048. A 24 week randomised double blind placebo controlled study to evaluate the atrophogenic potential of eflornithine in the treatment of women with excessive facial hair. //clinicaltrials.gov/show/NCT00152048 (accessed 3 September 2014).

NCT00451568 *{unpublished data only}*
NCT00451568. Metformin and oral contraceptives in PCOS. //clinicaltrials.gov/show/NCT00451568 (accessed 3 September 2014).

NCT00744510 *{unpublished data only}*
NCT00744510. Reflexology's effect on polycystic ovary syndrome (PCOS) (REPOS). //clinicaltrials.gov/show/NCT00744510 (accessed 3 September 2014).

NCT00746148 ***{unpublished data only}***

NCT00746148. Reflexology's effect on polycystic ovary syndrome: a pilot study (REPOS). //clinicaltrials.gov/show/NCT00746148 (accessed 3 September 2014).

NCT01051024 ***{unpublished data only}***

NCT01051024. Diamel in the treatment of polycystic ovary syndrome. //clinicaltrials.gov/show/NCT01051024 (accessed 3 September 2014).

NCT01396369 ***{unpublished data only}***

NCT01396369. Impact of flaxseed lignan (Brevail) on polycystic ovarian syndrome. //clinicaltrials.gov/show/NCT01396369 (accessed 3 September 2014).

NCT01555190 ***{unpublished data only}***

NCT01555190. Combination therapy with myo-inositol and folic acid versus myo-inositol alone: effects of six months treatment on clinical, endocrine and metabolic features in obese women with polycystic ovary syndrome. //clinicaltrials.gov/show/NCT01555190 (accessed 3 September 2014).

NCT01626443 ***{unpublished data only}***

NCT01626443. Role of myo-inositol and D-chiro Inositol on the ovaric and metabolic functions. //clinicaltrials.gov/show/NCT01626443 (accessed 3 September 2014).

NCT01791647 ***{unpublished data only}***

NCT01791647. Myo-inositol versus metformin in obese women with polycystic ovary syndrome. //clinicaltrials.gov/show/NCT01791647 (accessed 3 September 2014).

Additional references

Azziz 2003

Azziz R. The evaluation and management of hirsutism. *Obstetrics & Gynecology* 2003;**101**(5 Pt 1):995–1007. [PUBMED: 12738163]

Azziz 2004

Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen excess in women: experience with over 1000 consecutive patients. *Journal of Clinical Endocrinology & Metabolism* 2004;**89**(2):453–62. [PUBMED: 14764747]

Azziz 2006

Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *Journal of Clinical Endocrinology & Metabolism* 2006;**91**(11):4237–45. [PUBMED: 16940456]

Bailey 2014

Bailey A. What effect does metformin have on hirsutism and acne in women with polycystic ovary syndrome? 2014. www.evidence.nhs.uk (accessed 3 September 2014).

Barth 1993

Barth JH, Catalan J, Cherry CA, Day A. Psychological morbidity in women referred for treatment of hirsutism. *Journal of Psychosomatic Research* 1993;**37**(6):615–9. [PUBMED: 8410747]

Basow 1998

Basow SA, Braman AC. Women and body hair: social perceptions and attitudes. *Psychology of Women Quarterly* 1998;**22**:637–45.

Blume-Peytavi 2008

Blume-Peytavi U, Hahn S. Medical treatment of hirsutism. *Dermatologic Therapy* 2008;**21**(5):329–39. [PUBMED: 18844711]

Blume-Peytavi 2009

Blume-Peytavi U, Atkin S, Shapiro J, Lavery S, Grimalt R, Hoffmann R. European Consensus on the evaluation of women presenting with excessive hair growth. *European Journal of Dermatology* 2009;**19**(6):597–602. [PUBMED: 19726276]

Blume-Peytavi 2011

Blume-Peytavi U. An overview of unwanted female hair. *British Journal of Dermatology* 2011;**165**(Suppl 3):19–23. [PUBMED: 22171681]

Blume-Peytavi 2011b

Blume-Peytavi U, Vogt A. Current standards in the diagnostics and therapy of hair diseases - hair consultation. *Journal der Deutschen Dermatologischen Gesellschaft* 2011;**9**(5):394–410. [PUBMED: 21284803]

Blume-Peytavi 2013

Blume-Peytavi U. How to diagnose and treat medically women with excessive hair. *Dermatologic Clinics* 2013;**31**(1):57–65. [PUBMED: 23159176]

Bode 2012

Bode D, Seehusen DA, Baird D. Hirsutism in women. *American Family Physician* 2012;**85**(4):373–80. [PUBMED: 22335316]

Brodell 2010

Brodell LA, Mercurio MG. Hirsutism: Diagnosis and management. *Gender Medicine* 2010;**7**(2):79–87. [PUBMED: 20435271]

Brown 2006

Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. *BMJ* 2006;**333**(7572):804–6. [EMBASE: 2006511299]

Brown 2009

Brown J, Farquhar C, Lee O, Toomath R, Jepson RG. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD000194.pub2]

Caro 1996

Caro JJ, Caro G, O'Brien JA, et al. Assessing quality of life implication of depigmentation: the BASC scale. American Academy of Dermatology 54th Annual Meeting (Feb 10-15). Washington DC, 1996; Vol. 17.

Castelo-Branco 2010

Castelo-Branco C, Cancelo MJ. Comprehensive clinical management of hirsutism. *Gynecological Endocrinology* 2010;**26**(7):484–93. [PUBMED: 20218823]

Coffey 2006
Coffey S, Bano G, Mason HD. Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). *Gynecological Endocrinology* 2006;**22**(2):80–6. [PUBMED: 16603432]

Cook 2011
Cook H, Brennan K, Azziz R. Reanalyzing the modified Ferriman-Gallwey score: is there a simpler method for assessing the extent of hirsutism?. *Fertility & Sterility* 2011; **96**(5):1266–70. [PUBMED: 21924716]

Cosma 2008
Cosma M, Swiglo BA, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, et al. Clinical review: Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *Journal of Clinical Endocrinology & Metabolism* 2008;**93**(4):1135–42. [PUBMED: 18252787]

Costello 2007
Costello MF, Shrestha B, Eden J, Johnson N, Moran LJ. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD005552.pub2]

Domecq 2013
Domecq JP, Prutsky G, Mullan RJ, Hazem A, Sundaresh V, Elamin MB, et al. Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. *Journal of Clinical Endocrinology & Metabolism* 2013;**98**(12):4655–63. [PUBMED: 24092832]

Du 2012
Du Q, Yang S, Wang YJ, Wu B, Zhao YY, Fan B. Effects of thiazolidinediones on polycystic ovary syndrome: a meta-analysis of randomized placebo-controlled trials. *Advances in Therapy* 2012;**29**(9):763–74. [PUBMED: 22932791]

Du 2012b
Du Q, Wang YJ, Yang S, Wu B, Han P, Zhao YY. A systematic review and meta-analysis of randomized controlled trials comparing pioglitazone versus metformin in the treatment of polycystic ovary syndrome. *Current Medical Research & Opinion* 2012;**28**(5):723–30. [PUBMED: 22462531]

Dunaif 1992
Dunaif A, Givens JK, Haseltine F, Merriam GR. *The Polycystic Ovary Syndrome*. Cambridge, MA: Blackwell Scientific, 1992.

Egger 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34. [PUBMED: 9310563]

Ehrmann 2005
Ehrmann DA. Polycystic ovary syndrome. *New England Journal of Medicine* 2004;**352**(12):1223–36. [PUBMED: 15788499]

Ekbäck 2009
Ekbäck M, Wijma K, Benzein E. "It is always on my mind": women's experiences of their bodies when living with hirsutism. *Healthcare for Women International* 2009;**30**(5): 358–72. [PUBMED: 19350434]

Ekbäck 2011
Ekbäck M, Engfeldt P, Benzein E. "We feel rejected": experiences of women with hirsutism consulting physicians. *Journal of Psychosomatic Obstetrics & Gynaecology* 2011;**32** (3):157–9. [PUBMED: 21824045]

Escobar-Morreale 2010
Escobar-Morreale HF. Diagnosis and management of hirsutism. *Annals of the New York Academy of Sciences* 2010; **1205**:166–74. [PUBMED: 20840269]

Escobar-Morreale 2012
Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. *Human Reproduction Update* 2012;**18**(2):146–70. [PUBMED: 22064667]

Farquhar 2012
Farquhar C, Brown J, Marjoribanks J. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD001122.pub4]

Guerra-Tapia 2011
Guerra-Tapia A, Sancho Pérez B. Ethinylestradiol/chlormadinone acetate: dermatological benefits. *American Journal of Clinical Dermatology* 2011;**12**(Suppl 1):3–11. [PUBMED: 21895044]

Guyatt 2004
Guyatt G, Weaver B, Cronin L, Dooley JA, Azziz R. Health-related quality of life in women with polycystic ovary syndrome, a self-administered questionnaire, was validated. *Journal of Clinical Epidemiology* 2004;**57**(12):1279–87. [PUBMED: 15617954]

Guzel 2012
Guzel AI, Kuyumcuoğ lu U, Celik Y. Factors affecting the degree of hirsutism in patients with polycystic ovary syndrome. *Archives of Gynecology & Obstetrics* 2012;**285**(3): 767–70. [PUBMED: 21909749]

Haedersdal 2006
Haedersdal M, Gøtzsche PC. Laser and photoepilation for unwanted hair growth. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD004684.pub2]

Haedersdal 2011
Haedersdal M, Beerwerth F, Nash JF. Laser and intense pulsed light hair removal technologies: from professional to

home use. *British Journal of Dermatology* 2011;**165**(Suppl 3):31–6. [PUBMED: 22171683]

Hatch 1981
Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. *American Journal of Obstetrics & Gynecology* 1981;**140**(7):815–30. [PUBMED: 7258262]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Homburg 1996
Homburg R. Polycystic ovary syndrome-from gynaecological curiosity to multisystem endocrinopathy. *Human Reproduction* 1996;**11**(1):29–39. [PUBMED: 8671153]

Housman 2004
Housman TS, Derrow AE, Snively BM, Lahiry S, Rapp SR, Hawes DR, et al. Women with excessive facial hair: a statistical evaluation and review of impact on quality of life. *Cosmetic Dermatology* 2004;**17**(3):165. [EMBASE: 2004124038]

Hozo 2005
Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**:13. [PUBMED: 15840177]

Jing 2008
Jing Z, Liang-Zhi X, Tai-Xiang W, Ying T, Yu-Jian J. The effects of Diane-35 and metformin in treatment of polycystic ovary syndrome: an updated systematic review. *Gynecological Endocrinology* 2008;**24**(10):590–600. [PUBMED: 19012104]

Keegan 2003
Keegan A, Liao LM, Boyle M. 'Hirsutism': a psychological analysis. *Journal of Health Psychology* 2003;**8**(3):327–45. [PUBMED: 14670212]

Koulouri 2008
Koulouri O, Conway GS. A systematic review of commonly used medical treatments for hirsutism in women. *Clinical Endocrinology* 2008;**68**(5):800–5. [PUBMED: 17980017]

Koulouri 2009
Koulouri O, Conway GS. Management of hirsutism. *BMJ* 2009;**338**:b847. [PUBMED: 19329515]

Lanigan 2001
Lanigan SW. Management of unwanted hair in females. *Clinical Dermatology* 2001;**26**(8):644–7. [PUBMED: 11722446]

Legro 2013
Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism* 2013;**98**(12):4565–92. [PUBMED: 24151290]

Lipton 2006
Lipton MG, Sherr L, Elford J, Rustin MH, Clayton WJ. Women living with facial hair: the psychological and behavioral burden. *Journal of Psychosomatic Research* 2006; **61**(2):161–8. [PUBMED: 16880018]

Loo 2002
Loo WJ, Lanigan SW. Laser treatment improves quality of life of hirsute females. *Clinical & Experimental Dermatology* 2002;**27**(6):439–41. [PUBMED: 12372078]

Lorenzo 1970
Lorenzo EM. Familial study of hirsutism. *Journal of Clinical Endocrinology & Metabolism* 1970;**31**(5):556–67. [PUBMED: 4248490]

Lumachi 2010
Lumachi F, Basso SM. Medical treatment of hirsutism in women. *Current Medicinal Chemistry* 2010;**17**(23):2530–8. [PUBMED: 20491644]

Martin 2008
Martin KA, Chang J, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, et al. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism* 2008;**93**(4):1105–20. [PUBMED: 18252793]

Moran 2011
Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD007506.pub3]

Newcombe 1998
Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 1998;**17**(8):873–90. [PUBMED: 9595617]

O'Brien 1998
O'Brien SC, Lewis JB, Cunliffe WJ. The Leeds revised acne grading system. *Journal of Dermatological Treatment* 1998;**9** (4):215–20. [EMBASE: 1999025622]

Olsen 1999
Olsen EA. Methods of hair removal. *Journal of the American Academy of Dermatology* 1999;**40**(2 Pt1):143–55. [PUBMED: 10025738]

Paparodis 2011
Paparodis R, Dunaif A. The hirsute woman: challenges in evaluation and management. *Endocrine Practice* 2011;**17** (5):807–18. [PUBMED: 21856600]

Pasquali 2013
Pasquali R, Gambineri A. Therapy in endocrine disease: treatment of hirsutism in the polycystic ovary syndrome. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2013;**170**(2):R75–90. [PUBMED: 24272197]

Randall 2008
Randall VA. Androgens and hair growth. *Dermatologic Therapy* 2008;**21**(5):314–28. [PUBMED: 18844710]

RevMan 2014
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richards 1995
Richards RN, Meharg GE. Electrolysis: observations from 13 years and 140,000 hours of experience. *Journal of the American Academy of Dermatology* 1995;**33**(4):662–6. [PUBMED: 7673501]

Rosenfield 2005
Rosenfield RL. Clinical practice. Hirsutism. *New England Journal of Medicine* 2005;**353**(24):2578–88. [PUBMED: 16354894]

Rotterdam Criteria PCOS 2004
Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Human Reproduction* 2004;**19**(1):41–7. [PUBMED: 14711538]

Sadighha 2009
Sadighha A, Mohaghegh Zahed G. Meta-analysis of hair removal laser trials. *Lasers in Medical Science* 2009;**24**(1): 21–5. [PUBMED: 18027066]

Schulz 1995
Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12. [PUBMED: 7823387]

Shah 2009
Shah D, Patel S. Hirsutism. *Gynecological Endocrinology* 2009;**25**(3):140–8. [PUBMED: 19347703]

Somani 2008
Somani N, Harrison S, Bergfeld WF. The clinical evaluation of hirsutism. *Dermatologic Therapy* 2008;**21**(5):376–91. [PUBMED: 18844715]

Sonino 1993
Sonino N, Fava GA, Mani E, Belluardo P, Boscaro M. Quality of life in hirsute women. *Postgraduate Medical Journal* 1993;**69**(809):186–9. [PUBMED: 8497431]

Stedman 2011
Stedman MR, Curtin F, Elbourne DR, Kesselheim AS, Brookhart MA. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2011;**40**(6):1732–4. [PUBMED: 20026595]

Swiglo 2008
Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, et al. Clinical review: Antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *Journal of Clinical Endocrinology & Metabolism* 2008;**93**(4):1153–60. [PUBMED: 18252786]

Tang 2012
Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database of Systematic Reviews* 2012, Issue 5. [DOI: 10.1002/14651858.CD003053.pub5]

Teede 2006
Teede HJ, Hutchison S, Zoungas S, Meyer C. Insulin resistance, the metabolic syndrome, diabetes, and cardiovascular disease risk in women with PCOS. *Endocrine* 2006;**30**(1):45–53. [PUBMED: 17185791]

Tiggeman 1998
Tiggemann M, Kenyon SJ. The hairlessness norm: The removal of body hair in women. *Sex Roles* 1998;**39**(11-12): 873–85.

Treadwell 2006
Treadwell JR, Tregear SJ, Reston JT, Turkelson CM. A system for rating the stability and strength of medical evidence. *BMC Medical Research Methodology* 2006;**19**(6): 52. [PUBMED: 17052350]

van der Spuy 2003
van der Spuy ZM, Le Roux PA, Matjila MJ. Cyproterone acetate for hirsutism. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD001125]

van Zuuren 2012
van Zuuren EJ, Fedorowicz Z, Carter B, Andriolo RB, Schoones J. Interventions for female pattern hair loss. *Cochrane Database of Systematic Reviews* 2012, Issue 5. [DOI: 10.1002/14651858.CD007628.pub3]

Zawadski 1992
Zawadski JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, Merriam GR editor(s). *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific, 1992: 377–84.

References to other published versions of this review

van Zuuren 2013
van Zuuren EJ, Fedorowicz Z, Carter B. Interventions for hirsutism excluding laser and photoepilation therapy. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD010334]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmad 2008

Methods	Randomised, open-label, active-controlled trial Setting Centre of Diabetes and Endocrinology, Faculty of Medicine, Jawahar Lal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh, India Date of study Not reported. Duration of intervention 12 months
Participants	N = 70 Mean age = 23 years **Inclusion criteria of the trial** • Non-diabetic, euthyroid, normoprolactinemic women aged 18-35 years, attending the outpatient endocrinology clinic with complaints of menstrual irregularities, hirsutism, and/or sterility • PCOS diagnosed by the presence of (i) chronic ovulatory dysfunction-oligomenorrhoea (cycle length > 45 days) or amenorrhoea (cycle length > 6 months), (ii) evidence of hyperandrogenaemia, whether clinical (hirsutism with Ferriman-Gallwey (F-G) score $\geq$ 8) or biochemical (serum concentration of testosterone) and (iii) exclusion of other causes such as congenital adrenal hyperplasia (CAH), androgen secreting tumours, hyperprolactinaemia and Cushing's syndrome **Exclusion criteria of the trial** • History of diabetes mellitus, renal, hepatic or cardiovascular dysfunction • Medications known or suspected to affect reproductive or metabolic functions (e.g. clomiphene citrate, antiandrogens, oral contraceptive pills (OCPs) and anti-obesity compounds) within 6 months of study entry • Women who had undergone hysterectomy or oophorectomy Randomised N = 70 Withdrawals/losses to follow-up • 9/70 (13%); 4/35 in metformin group, 5/35 in rosiglitazone group • 2 conceived, 2 poor compliance, 2 incomplete data, 3 lost to follow-up Baseline data (mean (SD)) Hirsutism score (F-G): metformin group 10.52 (2.63); rosiglitazone group 9.55 (2.31) BMI (body mass index (kg/cm^2)) >30: metformin group (10), rosiglitazone group (9) 25-30: metformin group (14), rosiglitazone group (16) <25: metformin group (7), rosiglitazone group (7) Waist/hip ratio: metformin group 0.87 (0.06), rosiglitazone group 0.81 (0.02) Menstrual pattern Oligomenorrhoea: metformin group (18), rosiglitazone group (23) Amenorrhoea: metformin group (13), rosiglitazone group (7)
Interventions	**Intervention** • Metformin 850 mg b.i.d. for 12 months (35) **Comparator**

	• Rosiglitazone 2 mg b.i.d. for 12 months (35) Women were instructed not to change their dietary intake or exercise pattern during the study
Outcomes	Assessments (4): baseline, month 3, 6 and 12 **Outcomes of the trial** (as reported) 1. Homeostasis model insulin assessment resistance index (HOMA-IR) 2. Quantitative insulin sensitivity check index (QUICKI) 3. Area under the curve (AUC) for insulin and glucose 4. Evaluation of hyperandrogenaemia by clinical and biochemical parameters (hirsutism, ovulation, resumption of menstrual cycle, androgen levels) * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 39): "Subjects were randomly allocated into two group using random number tables" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 38): "open-label" Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 38): "open-label" Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/70 (13%), drop-outs or lost to follow-up, 4 in metformin group, 5 in rosiglitazone group, reasons reported. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias

Ahmad 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Aigner 2009

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Internal Medicine, General Hospital Oberndorf, Oberndorf, Austria Date of study Not reported. Duration of the intervention 3 months
Participants	N = 40 Mean age = 30 years **Inclusion criteria of the trial** • Women with PCOS diagnosed by the presence of: 1) long-standing ovulatory dysfunction (oligo- or amenorrhoea); 2) hirsutism (Ferriman-Gallwey score 7), and/or circulating serum total testosterone greater than 2.5 nmol/L and SHBG concentrations less than 50 nmol/L; and 3) exclusion of other endocrine disorders, e.g. thyroidal dysfunction, adrenal diseases, and hyperprolactinaemia **Exclusion criteria of the trial** • Desire for pregnancy or existing pregnancy • Basal FSH concentration greater than 20 IU/litre • Diabetes mellitus • Past hysterectomy • Intake of medication known or suspected to affect reproductive or metabolic function • History of liver disease and/or alcohol abuse, elevated liver enzymes • Severe uncontrolled illness Randomised N = 40 Withdrawals/losses to follow-up • 5/40 (13%); 3/20 pioglitazone group, 2/20 of placebo group; due to loss to follow-up and protocol violation Baseline data (mean (SEM)) BMI: pioglitazone group 29.4 (1.7), placebo group 27.5 (1.2) Waist/hip ratio: pioglitazone group 0.9 (0.1), placebo group 0.9 (0.0) Hirsutism score (F-G): pioglitazone group 15.5 (1.2), placebo group 15.6 (2.0) DHEAS (μmol/L): pioglitazone group 5.4 (0.6), placebo group 6.3 (0.6) Testosterone (nmol/L): pioglitazone group 2.4 (0.3), placebo group 2.8 (0.2) SHBG (nmol/L): pioglitazone group 36.8 (4.3), placebo group 40.9 (3.5) Free androgen index (FAI): pioglitazone group 9.3 (2.2), placebo group 8.5 (1.6)

Aigner 2009 (*Continued*)

Interventions	**Intervention** • Pioglitazone 30 mg once daily for 3 months (20) **Comparator** • Placebo once daily for 3 months (20)
Outcomes	Assessments (7): baseline, week 2, 4, 6, 8, 10, 12 **Outcomes of the trial** (as reported) 1. Serum concentration retinol-binding protein 4 2. Serum concentration adiponectin 3. Serum concentration visfatin 4. Serum concentration of total testosterone, SHBG, DHEAS, FSH, LH, progesterone, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, cholesterol, triglycerides, and liver enzymes * 5. BMI, waist/hip ratio and hirsutism score * 6. LHRH test with measurement of concentrations of LH and FSH after iv injection of 100 g LHRH 7. Oral glucose tolerance test 8. Homeostasis model assessment insulin resistance index (HOMA-IR) 9. Area under the curve (AUC) for insulin 10. The occurrence of ovulation was assessed for each patient by serial measurement of serum progesterone in combination with self reported menstruation. * Denotes outcomes prespecified for this review
Notes	Run-in phase before randomisation adhere to a written list of recommendations concerning a healthy diet and physical activity for weight maintenance during a period of 4 weeks while knowingly receiving placebo (run-in phase). This study used sera and data from Brettenthaler 2004. Data will be reported from only one of the 2 studies, whichever one provides the complete set

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1230): "...randomization was performed..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "according to the records the randomization was performed by the hospital pharmacy using a random number generator (such as used in EXCEL)" Comment: probably done

Aigner 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "Neither patients nor physicians knew about the allocation until the end of the trial." and "The pharmacy delivered "neutral" boxes or containers identical for verum and placebo with numbers, the numbers were generated in random order by the pharmacy and neither doctors nor patients knew the content nor the key." Comment: sequentially numbered drug containers of identical appearance; probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1230): "...(identical tablets, taken once daily) was begun. Patients and physicians were blinded to the applied treatment" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator-assessed as well as participant-assessed (menstruation) Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/40 (13%), 3 of pioglitazone group and 2 of placebo group, reasons unreported. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported

		Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 1234): "Support for this study from Land Salzburg (to W.P.) and Spar Austria (to C.D.) is gratefully acknowledged." Comment: we judged this as at a low risk of bias

Akalin 1991

Methods	Randomised, double-blind, placebo-controlled, cross-over trial Setting Section of Endocrinology, Department of Medicine, Hacettepe University, School of Medicine, Ankara, Turkey Date of study Not reported. Duration of intervention 6 months and then cross-over for 6 further months
Participants	N = 11 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute women **Exclusion criteria of the trial** • Not reported Randomised N = 11 Withdrawals/losses to follow-up • 2/11 (18%); lost to follow-up (1), pregnancy (1) Baseline data Cross-over; no separate data at start of each 6-month treatment period
Interventions	**Intervention** • Ketoconazole 600 mg once a day for 6 months **Comparator** • Placebo once a day for 6 months During the study all used non-hormonal contraception. Cross-over after 6 months, no wash-out period
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum testosterone, DHEAS, progesterone, estradiol, basal and stimulated cortisol and 17-alpha hydroxyprogesterone * 3. FSH and LH levels at 0, 30, 60, and 90 min of a GnRH stimulation test 4. Adverse effects *

Akalin 1991 (*Continued*)

	* Denotes outcomes prespecified for this review
Notes	No wash-out period. No separate data for first 6 months treatment period. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 20): "...dispensed randomly by the hospital pharmacy" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 20): "...dispensed randomly by the hospital pharmacy" Comment: form of central allocation. Probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 19): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 19): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	2/11 (18%), lost to follow-up (1), pregnancy (1) unclear in which treatment arm. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk

Akalin 1991 (*Continued*)

		of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

Al-Khawajah 1998

Methods	Randomised, active-controlled, dose-finding trial Setting Department of Medicine, King Saud University, Riyadh, Saudi Arabia Date of study Not reported. Duration of intervention 6 months
Participants	N = 45 Mean age = 25 years **Inclusion criteria of the trial** • Moderate to severe hirsutism **Exclusion criteria of the trial** • Drug treatment for hirsutism < 6 months prior to study entry • Signs of virilisation • Adrenal or ovarian neoplasm • Hyperprolactinaemia, congenital adrenal hyperplasia, Cushing's syndrome, or drug-induced hyperprolactinaemia Randomised N = 45 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SD)) F-G score: 22.4 (1.5) in 2.5 mg finasteride group; 20.3 (1.8) in 5 mg finasteride group, 21.0 (1.3) in 7.5 mg finasteride group
Interventions	**Intervention** • Finasteride 2.5 mg once a day for 6 months (15) **Comparator 1** • Finasteride 5 mg once a day for 6 months (15) **Comparator 2** • Finasteride 7.5 mg once a day for 6 months (15)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Serum testosterone, free testosterone, DHEAS, androstenedione, dihydrotestosterone (DHT), progesterone, prolactin, LH, FSH, cortisol * 2. Ferriman-Gallwey score * 3. Self assessment score; 5-point Likert scale * 4. Shaft diameter of anagen hairs from facial location

	* * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 19): "The patients were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Allen 2005

Methods	Randomised, active-controlled trial Setting Baystate Medical Center Children's Hospital, Tufts University School of Medicine, Springfield, MA, US Date of study Not reported. Duration of intervention 6 months
Participants	N = 35 Mean age = 15 years **Inclusion criteria of the trial** • Female adolescents aged 12 to 21 years with PCOS • Hyperandrogenaemia (total testosterone > 60 ng/dl and free testosterone > 1.1 pg/ml) with no evidence of androgen secreting tumour (no cliteromegaly, male body habitus, or total testosterone level > 200 ng/dl)) • Oligomenorrhoea (< 6 menses in the previous 6 months) • Obesity (> 95th percentile body mass index (BMI) for age) • Stimulated 17-hydroxyprogesterone < 300 ng/dl • Hyperinsulinaemic with a fasting insulin level > 20 μU/ml but not diabetic (fasting glucose level < 126 mg/dl) **Exclusion criteria of the trial** • Current or past sexual activity • OCP use within the previous 6 months, a positive urine pregnancy test (performed on all participants at baseline) • Abnormal blood urea nitrogen, creatinine, aspartate transaminase • Positive personal or family history of thrombosis Randomised N = 36 Withdrawals/losses to follow-up • 4/35 (11%); 2 in each group, unreachable (2), refused to attend to follow-up (2) Baseline data (mean (SEM)) BMI: OCP group 40.1 (2.1), metformin group 37.3 (1.3) Amenorrhoea/oligomenorrhoea: OCP group 4/11, metformin group 3/13 Acne score: OCP group 2.1 (0.53), metformin group 1.1 (0.40) F-G score: OCP group 12.4 (3.1), metformin group 8.4 (1.6)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + norgestimate 0.25 mg) for 6 months (17) **Comparator** • Metformin 500 mg b.i.d. for 2 weeks and then increased to 1 g b.i.d. up to 6 months (18)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Free testosterone level * 2. Ferriman-Gallwey score * 3. Menstrual rate * 4. Facial acne; Cook's numeric grading scale (0 to 8, higher is worse)

	* 5. Fasting insulin level and fasting glucose level 6. Lipid profile 7. Insulin sensitivity; fasting glucose/insulin ratio and QUICKI *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 763): "...the patient was randomly assigned, using concealed assignments generated from a random numbers table, to one of two groups" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 763): "using concealed assignments generated from a random numbers table..." After e-mail communication: "Allocation assignment for each subject number was marked on a paper, individually sealed in a concealing bank envelope by staff not involved in patient care or the clinical portion of the study prior to randomization of the first patient." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/35 (11%); 2 in each group, unreachable (2), refused to attend to follow-up (2). Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ashrafinia 2009

Methods	Randomised, active-controlled trial Setting Department of Gynecology and Obstetrics, Roointan-Arash Hospital, Tehran University of Medical Sciences, Tehran, Iran Date of study March 2006 until February 2008. Duration of intervention 6 months (metformin group)
Participants	N = 156 enrolled, 126 randomised Mean age = 26 years **Inclusion criteria of the trial** • Women between 15 to 45 years, with a history of infertility for at least 1 year and 3 treatment cycles with no response to clomiphene citrate • Eligibility of the women to participate in the trial was based on the following criteria according to the Rotterdam consensus (Rotterdam Criteria PCOS 2004): (1) irregular menstruation; (2) clinical and/or biochemical signs of hyperandrogenism; (3) polycystic ovaries (presence of 12 or more follicles in each ovary measuring 2 mm to 9 mm in diameter, and/or increased ovarian volume greater than 10 ml) **Exclusion criteria of the trial** • Diseases that would disturb clinical and hormonal responses (congenital adrenal hyperplasia, ovarian tumours, hyperprolactinaemia, or thyroid disease, Cushing syndrome and androgen-producing tumours) • Pregnancy during follow-up • BMI above 30 or below 17 Randomised N = 126 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SD)) BMI: metformin group 25.43 (2.79), laparoscopic ovarian diathermy group 25.54 (2.31) Testosterone (pg/cc): metformin group 1.42 (0.46), laparoscopic ovarian diathermy group 1.34 (0.48)
Interventions	Assessments (2): baseline, month 6 **Intervention** • Metformin 1500 mg/day for 6 months (63)

	Comparator • Laparoscopic ovarian diathermy (63)
Outcomes	**Outcomes of the trial** (as reported) 1. FSH, LH and testosterone * 2. Record of menstrual cycles * 3. Ferriman-Gallwey score * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 237): "...were randomly divided into 2 equal groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 237): "...using serially numbered opaque envelopes, for treatment with metformin or LOD" Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not feasible Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not feasible Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias

Ashrafinia 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Azziz 1995

Methods	Randomised, active-controlled trial Setting Departments of Obstetrics and Gynecology, University of Alabama, Birmingham, Alabama, US Date of study Not reported. Duration of the intervention 6 months
Participants	N = 22 Mean age = 30 years **Inclusion criteria of the trial** • Women of reproductive age complaining of hirsutism (Ferriman-Gallwey (F-G) score > 8) **Exclusion criteria of the trial** • Significant illness or contraindication to the use of OCP, oestrogen replacement, or leuprolide • 21-hydroxylase-deficient nonclassic adrenal hyperplasia, with adrenal or ovarian tumours • Hormonal medications within the previous 3 months Randomised N = 22 Withdrawals/losses to follow-up • 5/22 (23%); 2/11 in leuprolide 'plus' group, 3/11 in OCP group • 2 moved out of state (leuprolide 'plus' group), 3 side effects (OCP group) Baseline data BMI: leuprolide 'plus' group 32.0, OCP group 28.6 Waist/hip ratio: leuprolide 'plus' group 0.88, OCP group 0.82 F-G score: leuprolide 'plus' group 15, OCP group 12
Interventions	**Intervention** • Leuprolide 3.75 mg/month intramuscularly, 0.625 mg conjugated oestrogen and medroxyprogesterone acetate (10 mg) from days 1 to 12 of each month for 6 months (11) **Comparator** • OCP (ethinyl estradiol 35 μg + ethynodiol diacetate 1 mg) for 6 months (11)

Outcomes	Assessments (6): baseline, week 2, 4, 8, 12, and 28 **Outcomes of the trial** (as reported) 1. LH, FSH, estradiol, DHEAS, androstenedione, SHBG, and total and free testosterone * 2. Self assessment of hirsutism; questionnaire * 3. Ferriman-Gallwey score * 4. Facial hair density; photography * 5. Outer hair shaft diameter; microscopy * 6. Growth rate: photography and plucking * 7. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 3407): "Patients were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blind-

Azziz 1995 (*Continued*)

		ing
Incomplete outcome data (attrition bias) All outcomes	High risk	5/22 (23%); 2/11 in leuprolide 'plus' group, 3/11 in OCP group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 3408): "Leuprolide-ERT-treated patients were heavier than their OCP-treated counterparts and had a greater initial rate of hair growth" Comment: although this baseline difference is small, we judged this as at unclear risk of bias

Azziz 2001

Methods	Randomised, double-blind, placebo-controlled trial Setting Multi-centre, US Date of study Not reported. Duration of the intervention 44 weeks
Participants	N = 782 screened, 410 randomised Mean age = 29 years **Inclusion criteria of the trial** • Premenopausal women with suspected PCOS • PCOS was diagnosed by 1) the presence of chronic ovulatory dysfunction, defined as intermenstrual intervals of 45 days or more or a total of eight or fewer menses per year; 2) hyperandrogenaemia, defined as a serum level of free testosterone greater than the upper normal limit used in the central laboratory for this study (i.e. $\geq$ 21.8 pmol/L); and 3) the exclusion of other disorders, such as nonclassic adrenal hyperplasia, thyroid dysfunction, and hyperprolactinaemia **Exclusion criteria of the trial** • Unresolved medical conditions • Hysterectomy and/or oophorectomy • Type 1 or type 2 diabetes mellitus • Significant cardiovascular disease • Active cancer within the past 5 years • Participation in another investigational study within the past 30 days

	• The use of medications known or suspected to affect reproductive or metabolic functions within 60 days of study entry Randomised N = 410 (unclear how many to each arm) Withdrawals/losses to follow-up • 104/410 (25%) not completely clear how many from each group, with inconsistent totals of numbers and percentages • Early termination of the study by the sponsor (range 11.5% to 19.8%) and lack of compliance (range 5.0% to 13.6%). The percentage of patients withdrawing from the study due to adverse events ranged from 4% to 7%; this was not different between treatment arms Baseline data (mean (SEM)) N of hirsute women: troglitazone 150 mg group 56, troglitazone 300 mg group 55, troglitazone 600 mg group 62, placebo group 57 BMI: troglitazone 150 mg group 37.3 (8.3), troglitazone 300 mg group 35.3 (9.3), troglitazone 600 mg group 35.6 (8.3), placebo group 37.9 (8.3) Waist/hip ratio: troglitazone 150 mg group 0.89 (0.08), troglitazone 300 mg group 0.86 (0.08), troglitazone 600 mg group 0.88 (0.09), placebo group 0.89 (0.08) Number of cycles in the past 12 months: troglitazone 150 mg group 4.3 (3.1), troglitazone 300 mg group 4.4 (2.7), troglitazone 600 mg group 4.6 (3.0), placebo group 4.5 (2.7) Total testosterone (ng/ml): troglitazone 150 mg group 0.63 (0.04), troglitazone 300 mg group 0.64 (0.03), troglitazone 600 mg group 0.63 (0.03), placebo group 0.57 (0.03) Free testosterone (pg/ml): troglitazone 150 mg group 11.72 (0.73), troglitazone 300 mg group 11.55 (0.69), troglitazone 600 mg group 10.92 (0.56), placebo group 10.62 (0.61) Androstenedione (ng/ml): troglitazone 150 mg group 1.92 (0.08), troglitazone 300 mg group 2.09 (0.10), troglitazone 600 mg group 1.98 (0.07), placebo group 1.89 (0.08) SHBG (nmol/L): troglitazone 150 mg group 39.51 (2.56), troglitazone 300 mg group 41.39 (2.44), troglitazone 600 mg group 40.69 (2.18), placebo group 36.14 (2.03)
Interventions	**Intervention** • Troglitazone 150 mg/day for 44 weeks (78 = number that completed) **Comparator 1** • Troglitazone 300 mg/day for 44 weeks (77 = number that completed) **Comparator 2** • Troglitazone 600 mg/day for 44 weeks (78 = number that completed) **Comparator 3** • Placebo for 44 weeks (73 = number that completed) Participants were asked to follow a weight maintenance diet throughout the study to minimise the effect of weight changes on the disease state Participants in the study were requested not to use electrolysis, waxing, or plucking for removal of unwanted hair, except for treatment of lower legs and forearms
Outcomes	Assessments (7): baseline, week 4, 12, 20, 28, 36, 44 **Outcomes of the trial** (as reported) 1. Ovulatory function (by monitoring the urinary level of pregnanediol-3-glucuronide daily) * 2. Modified Ferriman-Gallwey score

	* 3. Hormonal levels (total and free testosterone, androstenedione, SHBG, LH, FSH, and the LH/FSH ratio) * 4. Measures of glycaemic parameters (fasting levels of glucose, insulin, haemoglobin A1c, and the glucose and insulin areas under the curve during an oral glucose challenge * Denotes outcomes prespecified for this review
Notes	Except for Ferriman-Gallwey scores, the N of participants for other outcomes were a combination of hirsute and non-hirsute women

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1627): "...eligible patients were randomized..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1627): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1627): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement

Incomplete outcome data (attrition bias) All outcomes	High risk	104/410 (25%), not completely clear how many from each group, with inconsistent totals of numbers and percentages. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 1826): "This work was supported by a grant from Parke-Davis Pharmaceutical Research." Five of the investigators were employed by Parke-Davis Pharmaceutical Research Comment: a potential risk of bias cannot be excluded

Badawy 2009b

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, Mansoura University, and a private practice setting, Mansoura, Egypt Date of study January 2005 until January 2007. Follow-up 6 months
Participants	N = 163 Mean age = 26 years **Inclusion criteria of the trial** • Women with clomiphene citrate resistant PCOS • Diagnosis of PCOS was based on the Rotterdam Criteria PCOS (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Not reported Randomised N = 163 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SD)) BMI: UTND group 29.3 (3.11), laparoscopic electrosurgery ovarian drilling group 28.2 (3.24) Duration in infertility in years: UTND group 3.2 (1.12), laparoscopic electrosurgery

Badawy 2009b (*Continued*)

	ovarian drilling group 28.2 (3.24) Menstrual cycle irregularities (%): UTND group 91.5, laparoscopic electrosurgery ovarian drilling group 88.9 Hyperandrogenism (%): UTND group 45.1, laparoscopic electrosurgery ovarian drilling group 40.7
Interventions	**Intervention** • Ultrasound-guided transvaginal needle ovarian drilling (UTND) (81) **Comparator** • Laparoscopic electrosurgery ovarian drilling (82)
Outcomes	Assessments (unclear): baseline, several times during each cycle up to 6 months **Outcomes of the trial** (as reported) 1. Hormonal changes (FSH, LH, T) * 2. Ovulation * 3. Pregnancy 4. Hirsutism and acne * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1165): "...randomly allocated to either treatment...using a computer-generated random table" Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "The method of concealment was sealed envelopes after computer-generated random table allocation." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done

Badawy 2009b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Banaszewska 2007

Methods	Randomised, open-label, active-controlled, cross-over trial Setting Department of Gynecology/Obstetrics, Poznan University of Medical Sciences, Poznan, Poland Date of study April until September 2004. Duration of intervention 12 weeks and then cross-over another 12 weeks
Participants	N = 54 screened, 48 randomised Mean age = 24 years **Inclusion criteria of the trial** • PCOS • PCOS was defined according to a recent Rotterdam European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM)-sponsored PCOS Consensus Workshop, i.e. in the presence of at least 2 of the 3 criteria: 1) oligo- or anovulation, 2) clinical and/or chemical signs of hyperandrogenism, and/or 3) polycystic ovaries; and exclusion of other aetiologies such as congenital adrenal hyperplasia, Cushing's syndrome, or androgen-secreting tumours **Exclusion criteria of the trial** • Conditions such as thyroid disease, hyperprolactinaemia, and diabetes mellitus • < 3 months before the study, use of any form of oral contraceptives, other steroid hormones, or any other treatments likely to affect ovarian function, insulin sensitivity,

	or lipid profile Randomised N = 48 Withdrawals/losses to follow-up • After cross-over 3/24 (13%) in simvastatin + OCP group Baseline data 45/48 had evidence of hyperandrogenism (Ferriman-Gallwey score ≥ 8 and/or hyperandrogenaemia (total testosterone ≥ 0.6 ng/ml); remaining 3 had acne)
Interventions	**Intervention** • Simvastatin 20 mg/day + OCP (ethinyl estradiol 20 µg + desogestrel 0.15 mg) for 12 weeks (24) **Comparator** • OCP for 12 weeks (24)
Outcomes	Assessments (3): baseline, week 12 and 24 **Outcomes of the trial** (as reported) 1. Total testosterone * 2. Free testosterone, DHEAS, SHBG, LH/FSH, LH/FSH ratio, prolactin * 3. Ferriman-Gallwey score * 4. Waist-hip ratio 5. BMI * 6. Total cholesterol, LDL, HDL, triglycerides 7. Fasting insulin, fasting glucose, insulin AUC, glucose AUC 8. QUICKI 9. Adverse effects * *Denotes outcomes prespecified for this review
Notes	As there was no wash-out period, we only included the first 3 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 457): "Randomization (open label) was performed in blocks of 10, using sealed envelopes" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 457): "using sealed envelopes" Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This

		was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 457): "open label" Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 457): "open label" Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	After cross-over 3/24 in simvastatin + OCP group were lost to follow-up. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 457): "Simvastatin was provided by Polfa Grodzisk Mazowiecki (Grodzisk Mazowiecki, Poland), whereas OCP was provided by Organon Polska (Warsaw, Poland)." and "Medications used in this study were obtained by donation from pharmaceutical companies: simvastatin was obtained from Polfa Grodzisk Mazowiecki and OCP was obtained from Organon Polska. Sponsors had no input into the study design, its execution, or interpretation of the findings." Comment: we judged this as at a low risk of bias

Banaszewska 2011

Methods	Randomised, active-controlled trial Setting Division of Infertility and Reproductive Endocrinology, Department of Gynecology, Obstetrics, and Gynecological Oncology, Poznan University of Medical Sciences, Poznan, Poland Date of study December 2006 until March 2009. Duration of intervention 6 months
Participants	N = 150 screened, 139 randomised Mean age = 46 years **Inclusion criteria of the trial** • PCOS • PCOS criteria as defined by the Rotterdam consensus and had at least 2 of the following: 1) clinical or chemical hyperandrogenism; 2) oligo- or amenorrhoea; and/or 3) polycystic ovaries as viewed by transvaginal ultrasound **Exclusion criteria of the trial** • Congenital adrenal hyperplasia • Elevated prolactin, thyroid disease, Cushing disease, or diabetes mellitus • < 3 months before the study oral contraceptives, other steroid hormones, or any other treatments likely to affect ovarian function, insulin sensitivity, or lipid profile Randomised N = 139 Withdrawals/losses to follow-up • 43/139 (31%); 20/48 in simvastatin group, 14/47 in metformin group, 8/44 in simvastatin + metformin group • Loss of telephone and mail contact; 11/48 in simvastatin group, 6/47 in metformin group, 5/44 in simvastatin + metformin group • Change of residence address; 6/48 in simvastatin group, 5/47 in metformin group, 2/44 in simvastatin + metformin group • Emigration; 4/48 in simvastatin group, 3/47 in metformin group, 1/44 in simvastatin + metformin group Baseline data (mean (SEM)) BMI: simvastatin group 23.5 (0.6), metformin group 24.7 (0.7), simvastatin + metformin group 24.8 (0.8) F-G score: simvastatin group 9.1 (0.3), metformin group 9.7 (0.3), simvastatin + metformin group 8.7 (0.3) Acne score: simvastatin group 1.19 (0.12), metformin group 1.21 (0.12), simvastatin + metformin group 1.55 (0.15) Total testosterone (ng/ml): simvastatin group 0.84 (0.03), metformin group 0.84 (0.04) , simvastatin + metformin group 0.85 (0.04) Free testosterone (ng/dl): simvastatin group 1.32 (0.09), metformin group 1.47 (0.10), simvastatin + metformin group 1.52 (0.10) DHEAS (μmol/L): simvastatin group 9.26 (0.42), metformin group 9.26 (0.41), simvastatin + metformin group 9.00 (0.49) SHBG (nmol/L): simvastatin group 49.3 (3.6), metformin group 41.4 (2.9), simvastatin + metformin group 40.3 (3.4)
Interventions	**Intervention** • Simvastatin 20 mg/day for 6 months (48) **Comparator 1**

	• Metformin 850 mg b.i.d. for 6 months (47) **Comparator 2** • Simvastatin 20 mg/day + metformin 850 mg b.i.d. for 6 months (44)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. BMI * 2. Ferriman-Gallwey score * 3. Acne score; 4-point Likert scale * 4. Transvaginal ultrasonographic examination 5. A 2-hour oral glucose tolerance test was performed with determinations of glucose and insulin in the fasting state as well as after a 75 g glucose load at 30, 60, 90, and 120 minutes 6. Insulin, total testosterone, free testosterone, 17-hydroxyprogesterone, LH, FSH, prolactin, SHBG, and DHEAS * 7. Total cholesterol and triglycerides, HDL and LDL cholesterol * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 3495): "Randomization was performed using 1:1:1 allocation ratio with blocks of random size (6, 9, or 12 subjects per block). Patient allocation and block size were obtained using random number tables." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 3495): "At the time of randomization, sequentially numbered, sealed envelopes were opened. Allocation to study group was concealed until a consent was obtained and inclusion/exclusion criteria verified. The randomization list was kept locked, and the allocation numbers were generated and sealed in the envelopes by one of the authors (R.Z.S.). Allocation of the patients was performed only by the author who was blinded to the randomization schedule." Comment: the report provides sufficient

		detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 3495): "Because commercially available pills were used, there was no blinding after randomization; consequently, investigators and patients could identify the actual treatment." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 3495): "Because commercially available pills were used, there was no blinding after randomization; consequently, investigators and patients could identify the actual treatment." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	43/139 (31%); 21/48 in simvastatin group, 14/47 in metformin group, 8/44 in simvastatin + metformin group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 3495): "Simvastatin (Simvachol) was obtained from Polfa Grodzisk (Grodzisk Mazowiecki, Poland) and metformin (Metformax) was provided by Polfa Kutno SA (Kutno, Poland)." and page 3500: "This work was supported by the Polish State Committee for Scientific Research (Grant KBN Nr 2PO5E 09630) and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant RO1 HD050656)" Comment: we judged this as at a low risk

		of bias

Barth 1991

Methods	Randomised, double-blind, active-controlled, dose finding trial Setting Department of Dermatology, Slade Hospital, Oxford, UK Date of study Not specified. Duration of intervention 12 months
Participants	N = 60 Mean age = 26 years **Inclusion criteria of the trial** • Hirsute women **Exclusion criteria of the trial** • No other medical problems • Not on OCP • Therapy that can cause acne of affect hair growth Randomised N = 60 Withdrawals/losses to follow-up • 22/60 (36.7%); 6/21 in Dianette + placebo group, 9/20 in Dianette + 20 mg cyproterone acetate group (CPA), 7/19 in Dianette + 100 mg CPA group • Depression; Dianette + placebo group (1), Dianette + 20 mg CPA group (2), Dianette + 100 CPA group (1) • Nausea; Dianette + placebo group (1) • Hypertension; Dianette + 20 mg CPA group (1) • Lack of effect; Dianette + placebo group (1), Dianette + 20 mg CPA group (1) • Rest lost to follow-up due to unknown reasons; Dianette + placebo group (3), Dianette + 20 mg CPA group (5), Dianette + 100 mg CPA group (6) Baseline data Ferriman-Gallwey Index: Dianette + placebo group 26, Dianette + 20 mg CPA group 26, Dianette + 100 CPA group 28 BMI: Dianette + placebo group 23.7, Dianette + 20 mg CPA group 24.1, Dianette + 100 CPA group 23.9 Testosterone (nmol/L): Dianette + placebo group 2.5, Dianette + 20 mg CPA group 2.8, Dianette + 100 CPA group 2.9
Interventions	**Intervention** • Dianette + placebo for 12 months (21) **Comparator 1** • Dianette + 20 mg CPA for 12 months (20) **Comparator 2** • Dianette + 100 mg CPA for 12 months (19)
Outcomes	Assessments: (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey Index *

	2. Linear hair growth and diameter with graduated capillary tube and optical micrometer 7 days after shaving * 3. Subjective assessments of hair growth on a linear analogue scale (7.5 cm positive, 7.5 cm negative) * 4. Side effects * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 6): "The hirsute women were allocated at random into three treatment groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 5-6): "...double-blind..." and "Individual dose regimens were blinded to both subjects and investigator" Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 5-6): "...double-blind..." and "Individual dose regimens were blinded to both subjects and investigator" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the

Barth 1991 (*Continued*)

		study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	22/60 (36.7%); 6/21 in Dianette + placebo group, 9/20 in Dianette + 20 mg cyproterone acetate group (CPA), 7/19 in Dianette + 100 mg CPA group, reasons reported. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 9): "We are grateful to Mrs M. A. Gales for the hormone assays, Mrs P. L. Yudkin for statistical advice and to Dr P. Longthome of Schering Health Care, Burgess Hill, West Sussex, UK for the supply and packaging of the medication." Comment: we judged this as at a low risk of bias

Battaglia 2010

Methods	Randomised, investigator-blinded, active-controlled pilot study Setting Department of Gynecology and Pathophysiology of Human Reproduction, University of Bologna, Italy Date of study January 2007 until June 2008. Duration of study 6 months
Participants	N = 40 Mean age = 24 years **Inclusion criteria of the trial** • > 18 years with PCOS referred to the clinic for treatment of hirsutism and contraceptive necessities • PCOS diagnosed as the presence of hirsutism (Ferriman-Gallwey score > 8), oligomenorrhoea or amenorrhoea, increased plasma circulating androgens, typical bilateral ultrasound (> 10 small-sized 2 mm to 10 mm subcapsular follicles, ovarian volume > 8 ml, and increased ovarian echogenicity), and colour Doppler findings (decreased resistances at level of stromal ovarian arteries) **Exclusion criteria of the trial**

	• The secondary causes of hyperandrogenism (hyperprolactinaemia and thyroid and adrenal disorders) • Ultrasound evidence of multi follicular ovaries • Smokers, regular intense exercise, hormone therapy < 6 months before the study. • Women with diabetes, renal or hepatic illness, and folic acid and vitamin B12 deficiencies • BMI > 30 kg/m^2, uterine malformations, endometriosis, ovarian functional cyst, unilateral ovarian resection, or ovariectomy Randomised N = 40 Withdrawals/losses to follow-up • 3/40 (8%); 1/20 drospirenone (DRSP) + EE group, 2/20 contraceptive vaginal ring group • Slight persistent headache; drospirenone + EE group (1) • Nausea and breast tenderness; contraceptive vaginal ring group (2) Baseline data (mean (SD)) BMI: DRSP + EE group 25.1 (4.3), contraceptive vaginal ring group 24.0 (4.2) Waist/hip ratio: DRSP + EE group 0.80 (0.08), contraceptive vaginal ring group 0.78 (0.08) F-G score: DRSP + EE group 12.2 (4.6), contraceptive vaginal ring group 13.3 (3.6) Androstenedione (nmol/L): DRSP + EE group 12.0 (3.2), contraceptive vaginal ring group 13.4 (3.3) Testosterone (nmol/L): DRSP + EE group 1.7 (0.7), contraceptive vaginal ring group 1. 8 (0.3) SHBG (nmol/L): DRSP + EE group 38 (16), contraceptive vaginal ring group 49 (11) FAI %: DRSP + EE group 5.1 (3.7), contraceptive vaginal ring group 4.5 (2.3)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) for 6 months (20) **Comparator** • Combined contraceptive vaginal ring (ethinyl estradiol 15 μg + etonogestrel 120 μg) (20)
Outcomes	Assessments (2): baseline, month 6 **Outcomes of the trial** (as reported) 1. Utero-ovarian ultrasound analysis and colour doppler evaluation of uterine and stromal ovarian arteries 2. Brachial Artery Flow-mediated vasodilatation 3. 24-hour ambulatory blood pressure monitoring 4. Fasting blood samples for testing biochemical and hormonal parameters (LH, FSH, testosterone, androstenedione, SHBG, LH/FSH ratio, FAI), nitrites/nitrates * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Battaglia 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote (page 1418): "The patients were randomly submitted" and "Randomization was performed by opening sequentially numbered sealed envelopes containing treatment allocation determined by a random number table" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1418): "...sequentially numbered sealed envelopes containing treatment allocation..." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1418): "The clinical examiners were blinded to the type of treatment" Comment: the report did not provide sufficient detail about the specific measures used to blind personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1418): "The clinical examiners were blinded to the type of treatment" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/40, reasons reported. Per-protocol analysis Comment: low and balanced number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Other bias	Low risk	The study appears to be free of other forms of bias

Batukan 2007

Methods	Randomised, investigator-blinded, active-controlled trial Setting Department of Obstetrics and Gynecology, Erciyes University School of Medicine, Kayseri, Turkey Date of study Not specified. Duration of intervention 12 months
Participants	N = 100 Mean age = 24 years **Inclusion criteria of the trial** • Moderate to severe hirsutism **Exclusion criteria of the trial** • Pregnancy • Androgen-secreting adrenal or ovarian neoplasm • Cushing's syndrome, or congenital adrenal hyperplasia • Combined oral contraceptives < 6 months prior to study entry Randomised N = 100 Withdrawals/losses to follow-up • 9/100 (9%); 2/50 in OCP including drospirenone (DRSP) group, 7/50 in OCP including CPA group • Lost to follow-up or pregnancy Baseline data PCOS: OCP including DRSP group (35), OCP including CPA group (30) Idiopathic hirsutism: OCP including DRSP group (13), OCP including CPA group (13) BMI: OCP including DRSP group 23, OCP including CPA group 21 Oligo/amenorrhoea: OCP including DRSP group (25), OCP including CPA group (26) Obese: OCP including DRSP group (12), OCP including CPA group (5) SHBG (nmol/L): OCP including DRSP group 35.8 (2.3), OCP including CPA group 40.7 (1.9) DHEAS (μg/ml): OCP including DRSP group 2.6 (0.2), OCP including CPA group 2.2 (0.1) Androstenedione (ng/ml): OCP including DRSP group 2.6 (0.1), OCP including CPA group 2.7 (0.1) Total testosterone (ng/dl): OCP including DRSP group 88.7 (4.4), OCP including CPA group 81.5 (5.1) Free testosterone (pg/ml): OCP including DRSP group 2.2 (0.2), OCP including CPA group 2.2 (0.2)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) for 12 months (50) **Comparator**

	• OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 12 months (50)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Serum total testosterone, free testosterone, androstenedione, DHEAS and SHBG levels * 2. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 39): "Patients were randomly assigned...according to a computer-based randomization sequence" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 39): "The same physician (I. I.M.), blinded to the treatment regimen.." and "Patients were not blinded to therapy. .." Comment: the report did not provide sufficient detail about the measures used to blind the investigator from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 39): "The same physician (I. I.M.), blinded to the treatment regimen... " Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement

Batukan 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	9/100 (9%); 2/50 in OCP including drospirenone group, 7/50 in OCP including CPA group. Per-protocol analysis Comment: low and balanced number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Bayhan 2000

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, Endocrinology, Public Health Faculty, Dicle University, Diyarbakir, Turkey Date of study Not specified. Duration of intervention 6 months
Participants	N = 60 Mean age = 22 years **Inclusion criteria of the trial** • Idiopathic hirsutism • Hirsutism defined as Ferriman-Gallwey score > 12 • Normal serum androgens (total testosterone, free testosterone, androstenedione, DHEAS) • No clinical or biochemical evidence of PCOS • Normal serum 17-OH progesterone levels • Normal ovulatory cycles **Exclusion criteria of the trial** • Adrenal or ovarian neoplasms • Hyperprolactinaemia • Cushing's syndrome • Congenital adrenal hyperplasia • PCOS • Drug-induced hyperandrogenism Randomised N = 60 Withdrawals/losses to follow-up • No losses to follow-up reported

	Baseline data (mean (SD)) F-G score: GnRH-a group 19 (3.5), finasteride group 17.7 (1.8) Total testosterone: GnRH-a group 0.8 (0.3), finasteride group 1.1 (1.0) Free testosterone: GnRH-a group 2.2 (0.9), finasteride group 2.3 (1.3) Androstenedione: GnRH-a group 2.2 (2.2), finasteride group 1.8 (1.2) DHEAS: GnRH-a group 237 (114), finasteride group 228 (99) SHBG: GnRH-a group 1.8 (0.7), finasteride group 1.6 (0.4)
Interventions	**Intervention** • GnRH agonist (depot leuprolide acetate) intramuscularly monthly over 6 months (30) **Comparator** • Finasteride 5 mg per os for 6 months (30) The GnRH agonist group received after 2 weeks oestrogen replacement
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum total testosterone, androstenedione, DHEAS, free testosterone, 17-hydroxyprogesterone, gonadotropins, estradiol, progesterone, SHBG * * Denotes outcomes prespecified for this review
Notes	Units are not provided for the hormones

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 203): "...were randomly assigned to receive..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Bayram 2002

Methods	Randomised, active-controlled trial Setting Departments of Endocrinology and Metabolism and 1Obstetrics and Gynecology, Faculty of Medicine, Erciyes University, Kayseri, Turkey Date of study Not specified. Duration of intervention 1 year
Participants	N = 56 Mean age = 23 years **Inclusion criteria of the trial** • Moderate to severe hirsutism (Ferriman-Gallwey score > 12) • Age range 18 to 41 years **Exclusion criteria of the trial** • Adrenal or ovarian neoplasm • Cushing's syndrome • Congenital adrenal hyperplasia • Prolactinoma • A history of drug-induced hyperandrogenism • Thyroid disorder • Hormonal medication known to influence hair growth or hormone levels < 6 months prior to study entry Randomised N = 56 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD))

	F-G score: 2.5 mg group 18.4 (4.6), 5 mg group 18.7 (5.2) BMI: 2.5 mg group 24.8 (4.7), 5 mg group 24.4 (4.4) Testosterone (ng/dl): 2.5 mg group 92.8 (42.1), 5 mg group 86.5 (49.0) Free testosterone (pg/ml): 2.5 mg group 3.0 (1.3), 5 mg group 3.4 (1.8) Androstenedione (ng/ml): 2.5 mg group 3.4 (1.7), 5 mg group 3.3 (1.4) SHBG (nmol/L): 2.5 mg group 49.1 (20.8), 5 mg group 43.4 (18.2) DHEAS (mg/dl): 2.5 mg group 271.5 (152.2), 5 mg group 285.2 (149.2)
Interventions	**Intervention** • Finasteride 2.5 mg a day for 1 year (29) **Comparator** • Finasteride 5 mg a day for 1 year (27) Patients were advised to avoid pregnancy during treatment because of possible feminisation of a male fetus. Sexually active women were advised to use barrier methods of contraception and oestrogens were not administered during the study
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. BMI * 3. Hormonal parameters (FSH, LH, estradiol, androstenedione, testosterone, free testosterone, 17α-hydroxy-progesterone, DHEAS, SHBG) * 4. Adverse events * 5. Menstrual cycle * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 468): "Patients were consecutively divided into two groups at random" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment,

Bayram 2002 (*Continued*)

		was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Beigi 2004

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, Arash Maternity Hospital, Tehran University of Medical Sciences, Tehran, Iran Date of study Not specified. Duration of intervention 9 months
Participants	N = 40 Mean age = 23 years **Inclusion criteria of the trial** • Hirsutism (Ferriman-Gallwey score ≥ 8) based on PCOS or idiopathic hirsutism • PCOS diagnosis was made on presence of 3 or more of the following criteria: hyperandrogenaemia, hirsutism, anovulatory or oligo-ovulatory cycles, polycystic ovaries on ultrasound, and LH/FSH ratio > 2; however, with the exclusion of other known disorders such as Cushing's syndrome, hyperprolactinaemia, or late-onset congenital adrenal hyperplasia **Exclusion criteria of the trial** • Hypertension • Signs of virilisation

	• Drug-induced hyperandrogenism • Evidence of thyroid dysfunction (abnormal free T4 or TSH) • Galactorrhoea and/or hyperprolactinaemia (abnormal prolactin levels) • Cushing's syndrome • Late-onset (non-classic) congenital adrenal hyperplasia Randomised N = 40 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: finasteride group 23.1 (2.5), CPA + EE2 group 23.4 (3.4) F-G score: finasteride group 23.7 (4.4), CPA + EE2 group 22.3 (4.2) Total testosterone (ng/dl): finasteride group 103 (45), CPA + EE2 group 99 (40) Free testosterone (pg/ml): finasteride group 4 (1), CPA + EE2 group 3.9 (1) Androstenedione (ng/ml): finasteride group 4 (0.9), CPA + EE2 group 4 (0.9) DHEAS (μg/dl): finasteride group 344.9 (120.6), CPA + EE2 group 348.8 (73.6) DHT (ng/dl): finasteride group 40.5 (14), CPA + EE2 group 39.4 (10.5) SHBG (nmol/L): finasteride group 85.5 (39.1), CPA + EE2 group 83.4 (35.4) PCOS: finasteride group 14/20, CPA + EE2 group 15/20 Regular menses: finasteride group 7/20, CPA + EE2 group 6/20
Interventions	**Intervention** • Finasteride 5 mg once a day for 9 months (20) **Comparator** • Cyproterone acetate 25 mg once a day on days 5 to 14 + ethinyl estradiol (EE2) 20 μg daily days 5 to 25 of the menstrual cycle for 9 months (20) Patients were advised to avoid pregnancy during treatment because of possible feminisation of a male fetus
Outcomes	Assessments (4): baseline, month 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Serum total and free testosterone, androstenedione, DHEAS, DHT, SHBG * 3. Adverse events * 4. Blood pressure, body weight, haematological evaluation, liver and renal function tests, lipid analyses * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 30): "Patients were randomly assigned..."

Beigi 2004 (*Continued*)

		Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Belisle 1986

Methods	Randomised, double-blind, active-controlled trial Setting Multi-centre (8) in Canada Date of study Not specified. Duration of intervention 12 months
Participants	N = 171 recruited, 158 randomised Age range = 18 to 40 years **Inclusion criteria of the trial** • Severe hirsutism (i.e. chief complaint of excessive hair growth and who, after

	appropriate clinical and para clinical investigation, required systemic therapy for such a condition) • Ferriman-Gallwey score > 14 • Age between 18 and 40 years • Ability to give consent to therapy and to remain in the study for 12 months. **Exclusion criteria of the trial** • Ovarian and adrenal tumours • Hormonal medications < 60 days prior to study entry • Other types of prescribed medication • Absolute contraindications to steroids. Randomised N = 158 Withdrawals/losses to follow-up 51/158 (32%); 29/79 in 2 mg CPA group, 22/79 in 100 mg group • Adverse events; 10/79 in 2 mg CPA group, 12/79 in 100 mg group • Patient-related; 2/79 in 2 mg CPA group, 4/79 in 100 mg group • Physician-related; 9/79 in 2 mg CPA group, 4/79 in 100 mg group • Preterm (> 4 weeks from end of study); 0/79 in 2 mg CPA group, 2/79 in 100 mg group • Loss to follow-up; 2/79 in 2 mg CPA group, 0/79 in 100 mg group Baseline data (mean) F-G score: 2 mg CPA group 19.5, 100 mg CPA group 20.1
Interventions	**Intervention** • OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg) for 12 months + placebo (79) **Comparator** • OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg) for 12 months + CPA 100 mg (79)
Outcomes	Assessments (6): baseline, month 1, 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. General complaints, endocrine and menstrual problems * 2. Weight, blood pressure 3. Ferriman-Gallwey score * 4. Serum total and free testosterone, FSH, LH, prolactin, androstenedione, DHEA and DHEAS * * Denotes outcomes prespecified for this review
Notes	There are inconsistencies regarding the number that dropped out. The investigators report that 51/158 dropped out, but data at 12 months suggest that there were still 56 participants in each group (which would mean 46/158 drop-outs)

Risk of bias

Bias	Authors' judgement	Support for judgement

Belisle 1986 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 1016): "They were then randomized and double-blindly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1016): "...double-blindly..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1016): "...double-blindly..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	51/158 (32%); 29/79 in 2 mg CPA group, 22/79 in 100 mg group, reasons reported. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Bhattacharya 2012

Methods	Randomised, double-blind, active-controlled trial Setting Department of Obstetrics and Gynaecology, S. C. Das Memorial Medical and Research Center, Jodhpur Park, Kolkata, India Date of study January 2010 until April 2011. Duration of intervention 12 months
Participants	N = 233 screened, 171 randomised Mean age = 22 years **Inclusion criteria of the trial** • PCOS according to criteria of Androgen Excess Society (Azziz 2006) • 18 to 35 years • History of oligomenorrhoea (< 6 menstrual cycles in 12 months) • Women with abnormal hair growth on their body **Exclusion criteria of the trial** • Cushing syndrome • Late-onset congenital adrenal hyperplasia • Gross hypothyroidism • Hyperprolactinaemia • Known contraindications for oestrogen therapy • Oral contraceptive pills in the preceding 3 months Randomised N = 171 Withdrawals/losses to follow-up 21/171 (12%); 9/58 in desogestrel group, 5/56 in CPA group, 7/57 in drospirenone (DRSP) group • Protocol violations; 2/58 in desogestrel group, 0/56 in CPA group, 3/57 in drospirenone group • Adverse events; 5/58 in desogestrel group, 2/56 in CPA group, 0/57 in drospirenone group • Unwillingness to continue; 2/58 in desogestrel group, 3/56 in CPA group, 2/57 in drospirenone group Baseline data (mean (SD)) BMI: desogestrel group 25.41 (4.49), CPA group 26.41 (3.81), DRSP group 26.47 (4.65) Waist-hip ratio: desogestrel group 0.80 (0.07), CPA group 0.83 (0.06), DRSP group 0.81 (0.07) Modified F-G score: desogestrel group 5.55 (4.51), CPA group 6.84 (5.17), DRSP group 6.14 (5.15) Testosterone (ng/ml): desogestrel group 0.44 (0.28), CPA group 0.53 (0.36), DRSP group 0.44 (0.27) SHBG (nmol/L): desogestrel group 32.05 (19.49), CPA group 23.85 (18.06), DRSP group 29.88 (19.88) FAI: desogestrel group 7.24 (8.78), CPA group 10.14 (7.91), DRSP group 7.48 (8.86)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) once a day for 12 months (58) **Comparator 1**

	• OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) once a day for 12 months (56) **Comparator 2** • OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) once a day for 12 months (57)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Free Androgen Index 2. HOMA-IR 3. Changes in the metabolic parameters 4. Changes in the SHBG and T levels * 5. BMI, modified Ferriman-Gallwey score, acne, acanthosis nigricans, and blood pressure * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1054): "...were then randomized into three intervention groups using computer-generated randomization tables in a 1:1:1 ratio..." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1054): "The intervention drugs were sealed in sequentially numbered identical opaque containers according to the allocation sequence." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1054): "The authors procured the medicines from the hospital pharmacy and the blinding was ensured by removing the commercial packing and putting the tablets in the opaque containers (i.e., after undoing the commercial packing) under the supervision of resident doctors (independently double checked) and nursing staff. The patients did not buy medicines directly and hence were blinded about the

		treatment groups. The entire process of random number generation, concealment, and sequential allocation were not disclosed to the investigators until the end of data collection." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator-assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21/171 (12%); 9/58 in desogestrel group, 5/56 in CPA group, 7/57 in drospirenone group, reasons reported. Intention-to-treat analysis Comment: we judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Breitkopf 2003

Methods	Randomised, double-blind, active-controlled trial Setting Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, USA Date of study Not specified. Duration of intervention 9 months
Participants	N = 47 Mean age = 34 years **Inclusion criteria of the trial** • Hirsutism (a cumulative Ferriman-Gallwey score of $\geq$ 10) **Exclusion criteria of the trial**

	• Androgen-secreting ovarian tumour (testosterone 200 ng/dl) • Congenital adrenal hyperplasia (17-hydroxyprogesterone 2 ng/ml) • Cushing's syndrome • OCPs within 2 months of enrolment • Long-acting progestins within 6 months of enrolment Randomised N = 47 Withdrawals/losses to follow-up 26/47 (55%); 12/23 EE + desogestrel group, 14/24 EE + levonorgestrel group • Lost to follow-up; 7/23 EE + desogestrel group, 9/24 in EE + levonorgestrel group • Adverse events; 2/23 EE + desogestrel group, 3/24in EE + levonorgestrel group • Ineffectiveness; 2/23 EE + desogestrel group, 1/24 in EE + levonorgestrel group • Discontinuation for reasons unrelated to medication; 1/24 EE + desogestrel group, 1/23 in EE + levonorgestrel group Baseline data (mean (SD)) Ferriman-Gallwey score: EE + desogestrel group 16.9 (3.9), EE + levonorgestrel group 14.7 (4.7) BMI: EE + desogestrel group 31.6 (7.9), EE + levonorgestrel group 31.7 (11.8) Total testosterone (ng/ml): EE + desogestrel group 56.7 (28.7), EE + levonorgestrel group 77.1 (60.0) Free testosterone (pg/ml): EE + desogestrel group 2.6 (1.5), EE + levonorgestrel group 2.6 (2.0) SHBG (nmol/L): EE + desogestrel group 21.5 (11.7), EE + levonorgestrel group 24.7 (15.5)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 μg + levonorgestrel 0.15 mg) for 9 months (24) **Comparator** • OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) for 9 months (23)
Outcomes	Assessments (4): baseline, months 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Adverse events (questionnaire) * 3. Participants' assessment (questionnaire) * 4. Serum total and free testosterone, DHEAS, androstenedione, 3-androstanediol glucuronide, SHBG, 17-hydroxyprogesterone and LH * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 350): "Subjects were randomized into two groups using block randomization by the pharmacy service at the University of Texas Medical Branch." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 350): "block randomization by the pharmacy service" Comment: central allocation (pharmacy-controlled randomisation). Probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 350): "The pills were identical in appearance in both groups." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator and participant-assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	26/47 (55%); 12/23 EE + desogestrel group, 14/24 in EE + levonorgestrel group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 352): "Funded by the American College of Obstetricians and Gynecologists/Organon Research Award in Contraception." Comment: a potential risk of bias cannot be excluded

Brettenthaler 2004

Methods	Randomised, double-blind, placebo-controlled trial Setting Division of Gynecological Endocrinology and Reproductive Medicine, University Women's Hospital Basel, Basel, Switzerland Date of study Not reported. Duration of the intervention 3 months
Participants	N = 40 Mean age = 30 years **Inclusion criteria of the trial** • Women with PCOS diagnosed by the presence of: 1) long-standing ovulatory dysfunction (oligo- or amenorrhoea); 2) hirsutism (Ferriman-Gallwey score 7) and/or circulating serum total testosterone greater than 2.5 nmol/L and SHBG concentrations less than 50 nmol/L; and 3) exclusion of other endocrine disorders, e.g. thyroidal dysfunction, adrenal diseases, and hyperprolactinaemia **Exclusion criteria of the trial** • Desire for pregnancy or existing pregnancy • Basal FSH concentration greater than 20 IU/L • Diabetes mellitus • Past hysterectomy • Intake of medication known or suspected to affect reproductive or metabolic function • History of liver disease and/or alcohol abuse, elevated liver enzymes • Severe uncontrolled illness Withdrawals/losses to follow-up • 5/40 (13%); 3/20 pioglitazone group, 2/20 of placebo group; due to loss to follow-up and protocol violation Baseline data (mean (SEM)) BMI: pioglitazone group 29.4 (1.7), placebo group 27.5 (1.2) Waist/hip ratio: pioglitazone group 0.9 (0.1), placebo group 0.9 (0.0) Hirsutism score (F-G): pioglitazone group 15.5 (1.2), placebo group 15.6 (2.0) DHEAS (μmol/L): pioglitazone group 5.4 (0.6), placebo group 6.3 (0.6) Testosterone (nmol/L): pioglitazone group 2.4 (0.3), placebo group 2.8 (0.2) SHBG (nmol/L): pioglitazone group 36.8 (4.3), placebo group 40.9 (3.5) Free androgen index (FAI): pioglitazone group 9.3 (2.2), placebo group 8.5 (1.6)
Interventions	**Intervention** • Pioglitazone 30 mg once daily for 3 months (20) **Comparator** • Placebo once daily for 3 months (20)
Outcomes	Assessments (7): baseline, week 2, 4, 6, 8, 10, 12 **Outcomes of the trial** (as reported) 1. Serum concentration of total testosterone, SHBG, DHEAS, FSH, LH, progesterone, LDL cholesterol, HDL cholesterol, cholesterol, triglycerides, and liver enzymes * 2. BMI, waist/hip ratio and hirsutism score * 3. LHRH test with measurement of concentrations of LH and FSH after iv injection

	of 100 g LHRH 4. Oral glucose tolerance test 5. Homeostasis model assessment insulin resistance index (HOMA-IR) 6. Area under the curve (AUC) for insulin 7. The occurrence of ovulation was assessed for each patient by serial measurement of serum progesterone in combination with self reported menstruation * * Denotes outcomes prespecified for this review
Notes	Run-in phase before randomisation adhere to a written list of recommendations concerning a healthy diet and physical activity for weight maintenance during a period of 4 weeks while knowingly receiving placebo (run-in phase). Aigner 2009 used sera and data reported in this study. Data will be reported from only one of the 2 studies, whichever one provides the complete set

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 3836): "...randomization was performed..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "according to the records the randomization was performed by the hospital pharmacy using a random number generator (such as used in EXCEL)." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "Neither patients nor physicians knew about the allocation until the end of the trial." and "The pharmacy delivered "neutral" boxes or containers identical for verum and placebo with numbers, the numbers were generated in random order by the pharmacy and neither doctors nor patients knew the content nor the key."

		Comment: sequentially numbered drug containers of identical appearance, probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 3836): "...(identical tablets, taken once daily) was begun. Patients and physicians were blinded to the applied treatment." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator-assessed as well as participant-assessed (menstruation) Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/40 (13%), 3 of pioglitazone group and 2 of placebo group, reasons unreported. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 3839): "This work was supported in part by a grant from the Medical Faculty of University of Basel and in part by an unrestricted educational grant from Takeda Pharma, Switzerland. N.B. was supported by a scholarship from the Schweizerische Eidgenössische Stipendienkommission." Comment: Takeda Pharma is the manufacturer of pioglitazone and a potential risk of bias cannot be excluded

Brown 2009B

Methods	Randomised controlled trial Setting Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA Date of study April 2003 until April 2005. Duration of intervention 12 weeks
Participants	N = 622 were screened, 37 randomised Mean age = 32 years **Inclusion criteria of the trial** • Pre-menopausal women with PCOS • ≤ 8 menses per year and clinical or biochemical evidence of hyperandrogenism (hirsutism with Ferriman-Gallwey score ≥ 8 or bio-available testosterone > 8.4 ng/dl (291.2 pmol/L, a value 2 standard deviations above the mean for the performing lab) • Sedentary lifestyle (defined as no regular exercise during a usual week) • Ability to come to the study exercise facility for monitored exercise • Agreement to maintain their current weight and dietary patterns for the study period. **Exclusion criteria of the trial** • Menopause • Hormonal contraceptive use • Antiandrogen therapy • Pregnancy (current or planned during the study period), recent breastfeeding • Congenital adrenal hyperplasia • Uncontrolled thyroid disease • Hyperprolactinaemia • Fasting hyperglycaemia (>125 mg/dl (6.9 mmol/l)) • Medication known to affect carbohydrate metabolism (metformin, thiazolidinediones) within the past 90 days • Unresolved medical conditions • History of malignancy other than non melanoma skin cancer in the past 5 years • Participation in another study within the past 30 days Randomised N = 37 Withdrawals/losses to follow-up • 17/37 (46%); 13/21 in exercise group, 4/16 in control group • Reasons for dropping out in exercise group; time constraints, injuries unrelated to exercise, pregnancy, major change in diet • Reasons for dropping out in control group; not reported Baseline data of study completers (median (interquartile range)) BMI: exercise group 37.9 (9.4), control group 31.3 (14.9) F-G score: exercise group 9.0 (16.0), control group 15.0 (8.0) Bioavailable testosterone (pmol/L): exercise group 319.0 (589.4), control group 450.7 (329.4)
Interventions	**Intervention** • Moderate-intensity exercise programme for 12 weeks, preceded by a ramp-up of 8 to 12 weeks (21) **Comparator** • No change in lifestyle for 12 weeks (16)

Outcomes	Assessments (2): baseline and week 12 **Outcomes of the trial** (as reported) 1. Lipoprotein profiles 2. Nuclear magnetic resonance spectroscopy to quantify particle size, total and subclass concentration of HDL, LDL, and VLDL * Denotes outcomes prespecified for this review
Notes	None of our outcomes were assessed, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 498): "Randomization was accomplished by generating a random sequence of two variables (for instance, As and Bs, representing the two treatment groups) using the online program at http://graphpad.com/quickcalcs/randomize2.cfm" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 498): "Each group assignment was placed in its own sequentially numbered envelope by an individual not involved in the study. Participants were assigned to a group based on these envelopes, and each participant had an equal chance of being randomized to either group." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not feasible Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not feasible Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	17/37 (46%); 13/21 in exercise group, 4/16 in control group. Reasons for drop-out only reported for exercise group. Per-protocol analysis

Brown 2009B (*Continued*)

		Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 503): "J.D.O. is employed by and is a stockholder of LipoScience Inc." The participants within the exercise group were older; 36.5 years versus 28 years Comment: a potential risk of bias cannot be excluded

Calaf 2007

Methods	Randomised, double-blind, active- and placebo-controlled trial Setting Multi-centre (14) in Spain Date of study Not reported. Duration of intervention 12 months
Participants	N = 131 Mean age = 24 years **Inclusion criteria of the trial** • Moderate to severe hirsutism (a score of > 15 in the modified Ferriman-Gallwey scale) hirsutism of either idiopathic or PCOS aetiology **Exclusion criteria of the trial** • Contraindication for oral hormonal contraception • Iatrogenic hirsutism • Ovarian or adrenal neoplasia • Prolactinoma • Cushing's syndrome • Congenital adrenal hyperplasia • Diabetes mellitus • Thromboembolic disease • Oral hormonal contraceptives or systemic treatment of their hirsutism over the last 3 months or those who had started a cosmetic treatment for fewer than 30 days before inclusion Randomised N = 131 Withdrawals/losses to follow-up • From the 131 women included, 12 patients did not satisfy the inclusion criteria, and so, even though they were considered in the safety evaluation, they were excluded from the efficacy evaluation. Of these 119 women, 77 women completed the study.

	Reasons unclear Baseline data (mean (SD)) BMI: flutamide 125 mg group 25.2 (3.28), flutamide 250 mg group 26.9 (7.88), flutamide 375 mg 27.3 (6.03), placebo group 25.4 (5.11) Waist/hip index: flutamide 125 mg group 0.81 (0.07), flutamide 250 mg group 0.80 (0.08), flutamide 375 mg 0.79 (0.09), placebo group 0.78 (0.09) Modified F-G score: flutamide 125 mg group 19.3 (3.36), flutamide 250 mg group 18.7 (2.64), flutamide 375 mg 18.0 (2.90), placebo group 18.4 (2.44) Acne score: flutamide 125 mg group 0.88 (0.88), flutamide 250 mg group 0.76 (1.15), flutamide 375 mg 0.76 (1.02), placebo group 0.84 (1.10) Seborrhoea score: flutamide 125 mg group 1.00 (1.00), flutamide 250 mg group 1.00 (1.04), flutamide 375 mg 0.91 (1.03), placebo group 0.97 (0.84)
Interventions	**Intervention** • Flutamide 125 mg + triphasic OCP for 12 months (25) **Comparator 1** • Flutamide 250 mg + triphasic OCP for 12 months (29) **Comparator 2** • Flutamide 375 mg + triphasic OCP for 12 months (34) **Comparator 3** • Placebo + triphasic OCP for 12 months (31)
Outcomes	Assessments (4): baseline, month 3, 6, and 12 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Acne and seborrhoea by the Cremoncini scale (for acne, a score of 1 indicates isolated pustules up to 10 in number, 2 indicates more than 10 isolated pustules, 3 indicates clusters of pustules, and 4 indicates confluent pustules; for seborrhoea, 1 indicates mild, 2 moderate, and 3 severe (Cremoncini 1976) * 3. Serum levels of prolactin, estradiol, testosterone, DHEAS, androstenedione, 17-hydroxyprogesterone, SHBG, free androgen index, LH, and FSH * 4. Adverse events * 5. Haematology and hepatic function evaluation, physical examination and biochemistry evaluation *Denotes outcomes prespecified for this review
Notes	12/131 randomised participants did not satisfy the inclusion criteria. These were included for safety evaluation, but not efficacy evaluation Triphasic OCP was 30 g, 40 g, and 30 g ethinyl estradiol and 50 g, 75 g, and 125g levonorgestrel

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (3447): "Patients were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 3447): "This study was carried out in double-blind conditions, and so neither the patient nor the doctor was aware of the composition of the treatment administered. For this purpose, preparation of the medication was performed in a centralized manner, and labeling, with the exception of the relevant randomization code, was identical in all four presentations." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	42/119 (35%) dropped out. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported

		Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 3452): "The study has been sponsored by Ipsen Pharma, S.A., Barcelona, Spain." Comment: Ipsen Pharma S.A. is the manufacturer of flutamide. A potential risk of bias cannot be excluded

Carmina 1994

Methods	Randomised, active-controlled trial Setting Cattedra di Endocrinologia, Universita di Palermo, Palermo, Italy Date of study Not reported. Duration of the intervention 6 months
Participants	N = 22 Mean age = 23 years **Inclusion criteria of the trial** • Hirsute women with hyperandrogenic chronic anovulation (HCA), aged 18 to 36 years with previous unsatisfactory treatment results for hirsutism • Diagnosis of HCA: chronic anovulation of premenarchal onset, hyperandrogenism (elevations in both serum testosterone and DHEAS), normal basal and ACTH-stimulated levels of serum 17-hydroxyprogesterone, and the absence of virilism and pelvic masses • Modified Ferriman-Gallwey (FG) score $\geq$ 8 **Exclusion criteria of the trial** • Not reported Randomised N = 22 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) F-G score: GnRH-A alone group 13.4 (1.5), GnRH-A + oestrogen/progesterone group 13.3 (1.0) Testosterone (nmol/L): GnRH-A alone group 4.13 (0.5), GnRH-A + oestrogen/progesterone group 3.64 (0.3) Free testosterone (pmol/L): GnRH-A alone group 25.7 (4.0), GnRH-A + oestrogen/progesterone group 23.2 (3.0) Androstenedione (nmol/L): GnRH-A alone group 16.4 (1.4), GnRH-A + oestrogen/progesterone group 14.7 (1.0) DHEAS (μmol/L): GnRH-A alone group 8.7 (1.6), GnRH-A + oestrogen/progesterone group 8.9 (1.1)
Interventions	**Intervention** • GnRH-A alone for 6 months (10) **Comparator**

Carmina 1994 (*Continued*)

	• GnRH-A + oestrogen + medroxyprogesterone for 6 months (12)
Outcomes	Assessments (2): baseline, month 6 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Serum, FSH, LH, testosterone, free testosterone, androstenedione, DHEAS, estradiol, osteocalcin, total cholesterol, HDL, triglycerides * 3. Pelvic sonography * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 126): "...patients were randomized to two different protocols..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias

Carmina 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Carmina 1998

Methods	Randomised, active-controlled trial Setting Practice in Italy Date of study Not reported. Duration of the intervention 1 year
Participants	N = 54 Mean age = 21 years **Inclusion criteria of the trial** • Women with hirsutism and hyperandrogenism • Ferriman-Gallwey-Lorenzo index ≥ 8 (Hatch 1981) **Exclusion criteria of the trial** • Tumours and adrenal enzymatic defects Randomised N = 54 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) Ferriman-Gallwey-Lorenzo index: dex (1 y) 16.5 (1.2), dex + spiro (1 y) 17.0 (1.2), dex + spiro (2 y) 17.7 (1.5), spiro (1 y) 16.8 (1.2) BMI: dex (1 y) 23.8 (1.0), dex + spiro (1 y) 24.5 (1.5), dex + spiro (2 y) 23.2 (1.2), spiro (1 y) 23.4 (1.2) Testosterone (ng/dl): dex (1 y) 88 (5), dex + spiro (1 y) 86 (7), dex + spiro (2 y) 92 (5), spiro (1 y) 80 (8) Unbound testosterone (pg/ml): dex (1 y) 4.6 (0.5), dex + spiro (1 y) 4.8 (0.6), dex + spiro (2 y) 5.0 (0.6), spiro (1 y) 4.6 (0.6) DHEAS (μg/ml): dex (1 y) 2.9 (0.4), dex + spiro (1 y) 3.0 (0.4), dex + spiro (2 y) 2.8 (0.5), spiro (1 y) 2.8 (0.5)
Interventions	**Intervention** • Dexamethasone 0.37 mg/day for one year (12) **Comparator** • Dexamethasone 0.37 mg/day plus spironolactone 100 mg/day for one year (18) **Comparator 2** • Dexamethasone 0.37 mg/day plus spironolactone 100 mg/day for two years (12) **Comparator 3**

Carmina 1998 (*Continued*)

	• Spironolactone 100 mg/day for one year (12)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey-Lorenzo scores * 2. Serum LH, FSH, testosterone, unbound testosterone, DHEAS, and 17-hydroxyprogesterone levels; and serum electrolytes * * Denotes outcomes prespecified for this review
Notes	The investigators of the study combined treatment arms with dexamethasone + spironolactone (1 and 2 years) in their analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 1076): "...the women were assigned randomly to..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias

Carmina 1998 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Carr 1995

Methods	Randomised, active-controlled trial Setting Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology and Center for Mineral Metabolism and Clinical Research, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas Date of study Not reported. Duration of the intervention 6 months
Participants	N = 52 recruited, 38 randomised Mean age = 27 years **Inclusion criteria of the trial** • Moderate to severe hirsutism (modified Ferriman-Gallwey score > 10) • 20 to 39 years **Exclusion criteria of the trial** • Ovarian or adrenal neoplasm • Prolactinoma • Cushing's syndrome • Congenital or adult onset adrenal hyperplasia (21-hydroxylase deficiency) • Drug-induced hirsutism • Steroids or other hormones < 2 months before screening Randomised N = 38 Withdrawals/losses to follow-up • 5/38 (13%); unclear from which groups, reasons unreported Baseline data (mean (SD)) F-G score: OCP group 21.7 (1.7), GnRH-a group 24.3 (1.4), OCP+GnRH-a 21.8 (1.7) Testosterone (nmol/L): OCP group 3.2 (1.33), GnRH-a group 2.3 (1.33), OCP+GnRH-a 3.0 (1.66) Free testosterone (pmol/L): OCP group 21.4 (10.61), GnRH-a group 15.5 (9.62), OCP+GnRH-a 18.6 (13.93) Androstenedione (nmol/L): OCP group 8.0 (2.32), GnRH-a group 7.2 (2.32), OCP+GnRH-a 13.0 (8.95) DHEAS (μmol/L): OCP group 4.8 (2.65), GnRH-a group 6.3 (6.63), OCP+GnRH-a 5.4 (1.99)

Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + norethindrone 1 mg) for 6 months (11 = N that completed the study) **Comparator 1** • GnRH-a 3.75 mg im every week for 6 months (11 = N that completed the study) **Comparator 2** • Combination of OCP and GnRH-a as stated above for 6 months (11 = N that completed the study)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Serum FSH, LH, estradiol, total testosterone, free testosterone, DHEAS, 17-hydroxyprogesterone, androstenedione * 2. Total cholesterol, total triglycerides, LDL, HDL, VLDL 3. Ferriman-Gallwey score * 4. Participants' assessment of hair growth and acne * 5. Hair diameter and vellus index * 6. Adverse events; participants' diary (hot flushes, headaches, vaginal dryness, breast tenderness, libido, irritability) * 7. Calciotropic hormones, estimated calcium balance, bone density studies * Denotes outcomes prespecified for this review
Notes	Data reported only for the 33 participants that completed the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1070): "the women were randomized into one of three treatment groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient informa-

Carr 1995 (*Continued*)

		tion to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/38 (13%); unclear from which groups, reasons unreported. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 1169): "This work was supported by NIH Grants ROl-HD-25860 and MOl-RR-00633" Comment: we judged this as at a low risk of bias

Cedeno 1990

Methods	Randomised, active-controlled trial Setting Endocrinology Unit, Hospital Universitario of Los Andes, Merida, Venezuela Date of study Not reported. Duration of the intervention 10 days
Participants	N = 18 Mean age = 23 years **Inclusion criteria of the trial** • History of severe acne and/or hirsutism, with or without disturbances in menses or obesity, and were thought to have PCO with hyperandrogenism • Diagnosis of PCO based on the presence of 3 or more of the following criteria: (1) persistent menstrual irregularities; (2) hirsutism or acne; (3) multicystic ovaries on ultrasonographic exploration; (4) luteinising hormone/follicle-stimulating hormone (LH/FSH) ratio $\geq$ 25 **Exclusion criteria of the trial** • Other endocrine disorders

	• Exogenous sex steroids, or other drugs which might affect lipoprotein metabolism < 10 days prior to study entry Randomised N = 18 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) Free testosterone (pg/ml): ketoconazole 400 mg group 12.15 (4.80), ketoconazole 800 mg group 14.91 (4.66) DHEAS (μg/ml): ketoconazole 400 mg group 444.95 (80.01), ketoconazole 800 mg group 443.00 (96.34) Androstenedione (ng/ml): ketoconazole 400 mg group 2.17 (0.45), ketoconazole 800 mg group 2.98 (0.56)
Interventions	**Intervention** • Ketoconazole 400 mg/day for 10 days (9) **Comparator** • Ketoconazole 800 mg/ day for 10 days (9) During the 10-day outpatient treatment programme, the patients followed their usual diets, exercise, smoking, and alcohol intake patterns
Outcomes	Assessments (2): baseline, day 10 **Outcomes of the trial** (as reported) 1. Serum lipids and lipoproteins and apoproteins 2. Serum free testosterone, DHEAS, androstenedione * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 511): "The PCO women were randomly divided into two groups of nine. .." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient informa-

Cedeno 1990 (*Continued*)

		tion to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 511): "Supported by CONICIT SI-1555, Caracas, Venezuela and by the Jewish Hospital Medical Research Council. Cincinnati Ohio." Comment: we judged this as at a low risk of bias

Cibula 2005

Methods	Randomised, active-controlled trial Setting Unit of Reproductive Endocrinology, Charles University, Prague, Czech Republic Date of study Not reported. Duration of intervention 6 months
Participants	N = 30 Mean age = 23 years **Inclusion criteria of the trial** • Women with PCOS • PCOS was defined as follows: (i) oligomenorrhoea from menarche (menstrual cycle 35 days); (ii) an increased concentration of at least one androgen above the upper reference limit (testosterone 0.5 to 2.63 nmol/L, androstenedione 1.57 to 5.4 nmol/L, dehydroepiandrosterone 0.8 to 10.5 nmol/L); and (iii) clinical manifestation of hyperandrogenism (acne, hirsutism, or both) **Exclusion criteria of the trial** • Secondary endocrine disorder, such as hyperprolactinaemia, thyroid dysfunction,

	or a non-classical form of congenital adrenal hyperplasia • Wishing to conceive within the next 6 months • Contraindications to oral contraceptive use Randomised N = 30 Withdrawals/losses to follow-up • 2/30 (7%); 0/15 OCP group, 2/15 OCP + metformin group • Reasons; adverse events (gastrointestinal problem) (1), non-compliance (1) Baseline data (mean (SD)) Waist/hip ratio: OCP group 0.75 (0.08), OCP + metformin group 0.79 (0.09) BMI: OCP group 22.1 (3.1), OCP + metformin group 24.7 (4.9) Testosterone (nmol/L): OCP group 3.94 (1.49), OCP + metformin group 4.84 (1.16) Androstenedione (nmol/L): OCP group 11.1 (5.8), OCP + metformin group 12.6 (3.5) DHEAS (μmol/L): OCP group 10.5 (2.2), OCP + metformin group 12.2 (3.8) SHBG (nmol/L): OCP group 32 (13), OCP + metformin group 27 (9)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + norgestimate 250 μg) for 6 months (15) **Comparator** • OCP (ethinyl estradiol + norgestimate 250 μg) + metformin 1500 mg/day for 6 months (15)
Outcomes	Assessments (2): baseline, month 6 **Outcomes of the trial** (as reported) 1. Serum LH, FSH, testosterone, DHEA, DHEAS) and androstenedione * 2. FAI 3. Plasma glucose concentration, plasma insulin concentration 4. Serum cholesterol and triglycerides 5. LDL and HDL 6. BMI * * Denotes outcomes prespecified for this review
Notes	Although one of the criteria for PCOS was clinical manifestation of hyperandrogenism (acne, hirsutism, or both), it was unclear how many women were hirsute. See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 181): "...randomly assigned to two groups using a generator of random values with a uniform distribution within the interval 0 to 1 (statistical software NCSS 2002). The values obtained were transformed into rank values." Comment: probably done

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/30 (7%); 0/15 in OCP group, 2/15 in OCP + metformin group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 184): "This study was supported by grant No. NH/6558-3 of the Internal Grant Agency of the Ministry of Health of the Czech Republic." Comment: we judged this as at a low risk of bias

Cicek 2003

Methods	Randomised, active-controlled trial Setting Selçuk University Faculty of Medicine Department of Obstetrics and Gynecology, Konya, Turkey Date of study Not reported. Duration of intervention 3 months
Participants	N = 50 Mean age = 25 years **Inclusion criteria of the trial** • Women with PCOS, according to clinical, hormonal, and ultrasonographic parameters, and had hyperandrogenism and complaints of hirsutism in spite of performed classical treatment with antiandrogens, oral contraceptives, and cyclic gestagens • PCOS diagnosis was based on: oligomenorrhoea beginning prepubertally (over the 35 days of the menstrual cycle length or < 6 menstrual cycles in 1 year), at least one high level of serum androgens, hirsutism and dens ovarian stroma and more than 10 follicles with 2 mm to 8 mm diameters shown by ultrasound scanning during the proliferate period **Exclusion criteria of the trial** • Adrenal, thyroid, pituitary, and hypothalamic endocrinological disorders • Diabetic patients • Women who did not receive classical PCOS treatment Randomised N = 50 Withdrawals/losses to follow-up • 8/50 (16%); 4/26 metformin group, 4/24 GnRH-a group • Adverse events; 3/26 metformin group • Pregnancy; 1/26 metformin group • Personal reasons; 4/24 GnRH-a group Baseline data (mean (SEM)) BMI: metformin group 26.6 (5.8), GnRH-a group 26.1(4.7) F-G score: metformin group 15.3 (1.3), GnRH-a group 15.5 (1.9) Total testosterone (ng/dl): metformin group 96.2 (46.5), GnRH-a group 115.5 (47.4) Free testosterone (pg/ml): metformin group 3.8 (2.5), GnRH-a group 3.7 (2.1) DHEAS (μg/dl): metformin group 251.9 (156.8), GnRH-a group 267.8 (106.2) SHBG (nmol/l): metformin group 40.4 (24.9), GnRH-a group 49.3 (12.4)
Interventions	**Intervention** • Metformin 850 mg b.i.d. for 3 months (26) **Comparator** • GnRH-a (goserelin) 3.6 mg/28 day for 3 months (24)
Outcomes	Assessments (2): baseline, month 3 **Outcomes of the trial** (as reported) 1. BMI, waist (cm), hip (cm) * 2. Ferriman-Gallwey score * 3. Serum FSH, LH, estradiol, total testosterone, free testosterone, DHEAS, 17OH-

	progesterone, progesterone, SHBG * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 108): "...were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8/50 (16%); 4/26 metformin group, 4/24 GnRH-a group. Reasons reported, per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Cicek 2003 (*Continued*)

Other bias	Low risk	The study appears to be free of other forms of bias

Ciotta 1995

Methods	Randomised, single-blinded, placebo-controlled trial Setting Department of Obstetrics and Gynecology, University of Catania, Italy Date of study Not reported. Duration of intervention 9 months
Participants	N = 18 Mean age = 20 years **Inclusion criteria of the trial** • Moderate to severe idiopathic hirsutism • Healthy, normal menses, normal BMI **Exclusion criteria of the trial** • Acne/seborrhoea or other sign of hyperandrogenism • Hormonal treatment < 6 months prior to study entry Randomised N = 18 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: finasteride group 20.8 (0.36), placebo group 20.7 (0.47) F-G score: finasteride group 19.0 (1.57), placebo group 21.8 (0.81) Total testosterone ng/ml: finasteride group 0.53 (0.05), placebo group 0.53 (0.01) Free testosterone (pg/ml): finasteride group 2.86 (0.11), placebo group 2.70 (0.08) Androstenedione (ng/ml): finasteride group 1.84 (0.12), placebo group 1.73 (0.16) Dihydrotestosterone (pg/ml): finasteride group 380.0 (29.4), placebo group 374.4 (37.2) DHEAS (μg/ml): finasteride group 2.02 (0.10), placebo group 2.08 (0.14) SHBG (μg/ml): finasteride group 2.17 (0.13), placebo group 2.22 (0.15)
Interventions	**Intervention** • Finasteride 7.5 mg/day for 9 months (9) **Comparator** • Placebo for 9 months (9) All participants were urged to use contraception barrier methods or an intrauterine device
Outcomes	Assessments (4): baseline, month 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Adverse event/evaluation of libido by both participants (interval scale), and investigators (semi structured talk on frequency of coitus) * 3. Serum FSH, LH, androstenedione, total and free testosterone, DHT, DHEAS,

	estradiol, 17OH-progesterone and SHBG * 4. Haematological evaluations, renal and liver functions *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 301): "... they were treated randomly and blindly" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 301): "... they were treated ... blindly" Comment: the report did not provide sufficient detail about the specific measures used to blind study participants or personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 301): "... they were treated ... blindly" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ciotta 2001

Methods	Randomised, double-blind, placebo-controlled trial Setting Reproductive Endocrinology Unit, University Hospital of Catania, Catania, Italy Date of study Not reported. Duration of intervention 3 months
Participants	N = 30 Mean age = 21 years **Inclusion criteria of the trial** • PCOS • PCOS diagnosed based on: menstrual abnormalities (< 6 periods in the last year), clinical manifestations of hyperandrogenism e.g. hirsutism, raised acne/seborrhoea scores, elevated serum total testosterone (> 80 ng/dl), and/or androstenedione (> 190 ng/dl), normal serum prolactin and normal thyroid function test, regular basal concentrations and/or normal response of 17 α-hydroxyprogesterone to the adrenocorticotrophic hormone stimulation test, BMI within normal range, normal glucose tolerance, elevated insulin response to OGTT **Exclusion criteria of the trial** • Not reported Randomised N = 30 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: acarbose group 22.84 (0.52), placebo group 22.70 (0.46) F-G score: acarbose group 20.93 (0.99), placebo group 19.07 (0.73) Acne/seborrhoea score: acarbose group 2.10 (0.15), placebo group 1.80 (0.14) Testosterone (nmol/L): acarbose group 3.33 (0.10), placebo group 3.19 (0.10) Androstenedione (nmol/L): acarbose group 8.69 (0.42), placebo group 8.73 (0.45) DHEAS (µmol/L): acarbose group 7.17 (0.42), placebo group 7.08 (0.40) SHBG (nmol/L): acarbose group 41.1 (2.5), placebo group 35.6 (2.1)
Interventions	**Intervention** • Acarbose 300 mg/day for 3 months (15) **Comparator** • Placebo for 3 months (15)

Ciotta 2001 (*Continued*)

Outcomes	Assessments (2): baseline and month 3 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Acne/seborrhoea score * 3. Serum FSH, LH testosterone, androstenedione, DHEAS, prolactin, 17OH-progesterone, SHBG * 4. BMI * 5. Adverse events * * Denotes outcomes prespecified for this review
Notes	Study also included 15 healthy controls

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2067): "...randomly divided. .." and "Randomization was achieved by a computer generated list." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 2067): "...the study was conducted in a double-blind fashion..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 2067): "...the study was conducted in a double-blind fashion..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the

Ciotta 2001 (*Continued*)

		study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ciotta 2012

Methods	Randomised, double-blind, active- and placebo-controlled trial Setting Institute of Obstetric and Gynaecological Pathology, Santo Bambino Hospital, University of Catania, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 111 Mean age = 25 years **Inclusion criteria of the trial** • PCOS, characterised by oligomenorrhoea and/or acne, and/or mild hirsutism (< 15 on Ferriman-Gallwey score), insuline resistance **Exclusion criteria of the trial** • Not reported Randomised N = 111 Withdrawals/losses to follow-up • Not reported Baseline data Nothing reported
Interventions	**Intervention** • Myo-inositol 2 g (+ folic acid) b.i.d. for 6 months (40) **Comparator 1** • D-chiro-inositol 500 mg (+ folic acid, B12 vitamin and manganese) b.i.d. for 6 months (42) **Comparator 2** • Multivitamin placebo without folic acid, B12 vitamin, and manganese b.i.d. for 6 months (29)

Outcomes	Assessments (2): baseline, month 6 **Outcomes of the trial** (as reported) 1. Menstrual cycle * 2. Acne score * 3. Hirsutism score (Ferriman-Gallwey) * 4. Metabolic parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glycaemia, insulinaemia and HOMA-IR) 5. Endocrine Parameters (LH, FSH, prolactin, total testosterone, free testosterone, androstenedione, 17-OH-P, DHEA, DHEAS, SHBG) * * Denotes outcomes prespecified for this review
Notes	Poster, limited data provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page S545): "...randomized..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page S545): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page S545): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the

Ciotta 2012 (*Continued*)

		study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

Ciotta 2012B

Methods	Randomised, double-blind, placebo-controlled trial Setting Institute of Obstetric and Gynaecological Pathology, Santo Bambino Hospital, University of Catania, Italy Date of study Not reported. Duration of intervention 3 months
Participants	N = 58 Mean age = 27 years **Inclusion criteria of the trial** • PCOS based on oligo- or amenorrhoea (< 6 menstrual cycles per year), hyperandrogenism (hirsutism or alopecia), hyperoestrogenaemia (elevated levels of total or free testosterone), typical feature of ovaries on ultrasound scan **Exclusion criteria of the trial** • Not reported Randomised N = 58 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean) No separate data per group BMI: 28 Waist/hip ratio: 0.87 Acne score: 3.5 F-G score: 15
Interventions	**Intervention** • D-chiro-inositol 250 mg in combination with manganese, folic acid, and vitamin B12 b.i.d. for 3 months (38) **Comparator** • Multivitamin b.i.d. for 3 months (20)

Outcomes	Assessments (2): baseline, month 3 **Outcomes of the trial** (as reported) 1. BMI * 2. Waist/hip ratio 3. Acne score (Cremoncini 1976) * 4. Hirsutism score (Ferriman-Gallwey) * 5. Blood pressure 6. Menstrual cycles * 7. Serum LH, FSH, estradiol, total and free testosterone, androstenedione, DHEAS, 17OH progesterone, SHBG, prolactin, thyroid function * 8. Glycaemia, cholesterol, triglycerides, blood urea nitrogen, basal insulin 9. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 146): "...according to a randomization table..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 146): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 146): "...double-blind..." Comment: uncertainty about the effective-

Ciotta 2012B (*Continued*)

All outcomes		ness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	High risk	Although the authors conducted clinical and endocrine evaluations the following outcomes were either not reported or inadequately reported: hirsutism score, BMI, waist/hip ratio, and blood pressure values Comment: we judged this as at a high risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Consoli 1994

Methods	Randomised, active-controlled trial Setting Endocrinology Department, Hospital Saint-Louis, Paris, France Date of study Not reported. Duration of intervention 12 months
Participants	N = 67 Mean age = 26 years **Inclusion criteria of the trial** • Hirsutism and/or other signs of hyperandrogenism **Exclusion criteria of the trial** • Not reported Randomised N = 67 Withdrawals/losses to follow-up • 13/67 (19%); reasons not reported Baseline data Not reported per group. Only 33/67 had hirsutism
Interventions	**Intervention** • Cyproterone acetate 50 mg + estradiol valerate 2 mg per os for 12 months (28) **Comparator** • Cyproterone acetate 50 mg + transdermal estradiol 50 mg for 12 months (26)

Outcomes	Assessments (2): baseline and month 12 **Outcomes of the trial** (as reported) 1. Quality of life (11 questions); 4-point Likert scale * 2. Acceptance; visual analogue scale (VAS) 3. Tolerance; questionnaire * 4. Hirsutism score * * Denotes outcomes prespecified for this review
Notes	Distribution of participants to either intervention group unclear; no separate data reported for participants with hirsutism, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 784): "Après randomisation.. .". Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	13/67 (19%); reasons not reported. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias

Consoli 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	There was baseline imbalance in BMI: higher in transdermal estradiol group (23.4) compared to oral estradiol group (21.0) . One of the investigators was employed by Schering, the manufacturer of cyproterone acetate, the transdermal estradiol, and the oral estradiol Comment: we judged this as at a high risk of bias

Couzinet 1986

Methods	Randomised, active-controlled, cross-over trial Setting Service d'Endocrinologie et des Maladies de la Reproduction Hopital de Bicetre, Bicetre, France Date of study Not reported. Duration of intervention 3 months, wash-out period of 6 months and then again 3 months intervention
Participants	N = 10 Age range 20 to 35 years **Inclusion criteria of the trial** • Clinical and biochemical criteria for PCOS • > 120% of ideal body weight • Hirsutism • Oligo- or amenorrhoea with progesterone (P)-induced withdrawal bleeding • Evidence of PCOS by ultrasound • Serum androstenedione > 2.3 ng/ml and a LH/FSH ratio > 3 • Plasma prolactin levels were normal **Exclusion criteria of the trial** • Not reported Randomised N = 10 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) Testosterone (ng/ml): CPA group 1.0 (0.11), dTrp^6-LHRH group 1.10 (0.10) Androstenedione (ng/ml): CPA group 2.81 (0.23), DTrp^6-LHRH group 2.44 (0.14)

Couzinet 1986 (*Continued*)

Interventions	**Intervention** • Cyproterone acetate 50 mg for 3 months and then 6 months later cross-over **Comparator** • 6-D tryptophane LHRH for 3 months and then 6 months later cross-over All patients were asked to eat a 1200 kcal/day diet
Outcomes	Assessments (4): baseline, month 1, 2, and 3 **Outcomes of the trial** (as reported) 1. Acne and seborrhoea (Cremoncini 1976) * 2. Ferriman-Gallwey score * 3. Pelvic ultrasound 4. Serum estradiol, testosterone, androstenedione, DHEAS * 5. 3αandrostanediol in 24-hour urine sample 6. LHRH test *Denotes outcomes prespecified for this review
Notes	Although the wash-out period of 6 months was considered adequate, there were no end data for first treatment period, nor baseline data for second treatment period. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1031): "The sequence of drug administration was randomly allocated in a cross-over fashion for the 10 patients" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Couzinet 1986 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 1034): "We are also most grateful to Dr. R. Y. Mauvernay (Debiopharm, Lausanne, Switzerland) and Dr. Deschamps de Paillette (Laboratoire Beaufour, Paris, France) for their kind arrangements for the supply of microcapsules." Comment: we judged this as at a low risk of bias

Crave 1995

Methods	Randomised, double-blind, placebo-controlled trial Setting Hospices Civils de Lyon, Lyon, France Date of study Not reported. Duration of intervention 4 months
Participants	N = 24 Mean age = not reported **Inclusion criteria of the trial** • Hirsutism • BMI > 25 kg/m^2 **Exclusion criteria of the trial** • Concomitant diseases • Medication prior to study entry • Contraindication to metformin Randomised N = 24 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: metformin group 35.2 (1.2), placebo group 32.7 (1.5)

Crave 1995 (*Continued*)

	F-G score: metformin group 17 (2), placebo group 9 (3)
Interventions	**Intervention** • Metformin once daily 850 mg for the first week to 850 mg twice daily for subsequent 15 weeks **Comparator** • Placebo for 4 months Each patient was required to follow a detailed and specific low fat and low calorie diet (1500 cal/day with 30% fat) for 4 months
Outcomes	Assessments (3): baseline, month 2 and 4 **Outcomes of the trial** (as reported) 1. Height, weight, BMI, waist/hip ratio * 2. Plasma lipids, SHBG, corticosteroid-binding globulin, androgen levels * 3. Glucose, insulin, oral glucose tolerance test, AUC glucose, AUC insulin 4. Evaluation of total energy intake * Denotes outcomes prespecified for this review
Notes	Unclear how many participants started in each treatment arm. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2058): "Metformin (Lipha Sante, Aron-Medicia Division, Lyon, France) and placebo were given in a randomized, double blind design." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 2058): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of participants/healthcare providers during the study. Insufficient information to permit a clear

Crave 1995 (*Continued*)

		judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 2058): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 2057): "This work was supported by a grant from Lipha Santé (Division Aron Medicia)." Lipha Santé is the manufacturer of metformin Baseline imbalance in F-G score, quote (page 2058): "...in the metformin group, the hirsutism score was higher ($P < 0.03$) than that in the placebo group (17 (2) vs 9 (3)), and in the placebo group, the mean plasma A (androstenedione) concentration was higher ($P < 0.04$) than that in the metformin group." Comment: we judged this as at a high risk of bias

Creatsas 1993

Methods	Randomised, active-controlled trial Setting 1st Department of Obstetrics and Gynecology, "Alexandra" Hospital, Division of Pediatric-Adolescent Gynecology, University of Athens, Greece Date of study Not reported. Duration of intervention 6 months
Participants	N = 45 Mean age = 17 years **Inclusion criteria of the trial** • Oligomenorrhoeic adolescents with PCOS with menstrual intervals of 40 to 65

	days **Exclusion criteria of the trial** • Not reported Randomised N = 45 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean SEM): BMI: EE + CPA group 22.8 (1.1), DTr6 LHRH group 23.6 (1.1) F-G score: EE + CPA group 10.9 (0.5), DTr6 LHRH group 11.6 (0.9) Testosterone (nmol/L): EE+ CPA group 3.3 (0.2), DTr6 LHRH group 3.1 (0.2) Androstenedione (ng/ml): EE+ CPA group 2.9 (0.6), DTr6 LHRH group 3.1 (0.7) SHBG (nmol/L): EE+ CPA group 42.2 (2.8), DTr6 LHRH group 45.4 (3.7) DHEAS (μmol/ml): EE+ CPA group 2.8 (0.5), DTr6 LHRH group 3.2 (0.2)
Interventions	**Intervention** • OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg) for 6 months (31) **Comparator** • D-Tr-6-LHRH 3.75 mg given intramuscularly every 28 days for 6 months (14)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. BMI * 2. Waist-hip circumference 3. Ultrasound of ovarian volume, uterine area 4. Clinical characteristics of menstrual period * 5. Ferriman-Gallwey score * 6. Serum FSH, LH, 17β-estradiol, prolactin, testosterone, SHBG, androstenedione, DHEAS * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 148): "...were randomly allocated..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Creatsas 1993 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Creatsas 2000

Methods	Randomised, active-controlled trial Setting Athens University, 2nd Department of Obstetrics and Gynecology, Athens, Greece Date of study Not reported. Duration of intervention 12 months
Participants	N = 24 Mean age = 17 years **Inclusion criteria of the trial** • Clinical signs of PCOS (oligomenorrhoea, secondary amenorrhoea and/or hirsutism) • Normal thyroid function • Normal prolactin levels **Exclusion criteria of the trial** • Congenital adrenal hyperplasia

	• Hormonal medication (including OCP) < prior to study Randomised N = 24 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: desogestrel + EE group 24.9 (4.7), CPA + EE group 23.4 (3.8) F-G score: desogestrel + EE group 16.2 (6.2), CPA + EE group 16.8 (4.7) Testosterone (ng/ml): desogestrel + EE group 1.06 (0.3), CPA + EE group 0.9 (0.3) Free testosterone (pg/ml): desogestrel + EE group 3.2 (0.9), CPA + EE group 2.9 (0.6) Androstenedione (ng/ml): desogestrel + EE group 3.9 (0.9), CPA + EE group 3.6 (1) SHBG (nmol/L): desogestrel + EE group 70 (51), CPA + EE group 67 (40)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) for 12 months (12) **Comparator** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 12 months (12)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Lipid profile (triglycerides, total cholesterol, LDL, HDL, apolipoproteins A-I, A-II, B and lipoprotein (a)) *Denotes outcomes prespecified for this review
Notes	No final values reported for F-G score, PI did not reply. No usable data, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 250): "...were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement

Creatsas 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Cusan 1994

Methods	Randomised, active-controlled trial Setting Medical Research Group in Molecular Endocrinology, Centre Hospitalier de l'Université Laval Research Center, Quebec, Canada Date of study Not reported. Duration of intervention 9 months
Participants	N = 53 Mean age = 26 years **Inclusion criteria of the trial** • Premenopausal women with moderate to severe hirsutism **Exclusion criteria of the trial** • Adrenal or ovarian tumours • Concomitant disease • Medication < 6 months prior to study entry Randomised N = 53 Withdrawals/losses to follow-up • 5/53 (9%); 1/28 flutamide group, 4/27 spironolactone group, reasons unreported Baseline data (mean (SEM)) All participants had a F-G score ≥ 14 BMI: flutamide group 26.2 (1.3), spironolactone group 27.3 (1.4) Normal/abnormal menses: flutamide group 15/13, spironolactone group 14/13

	F-G score: flutamide group 25 (1.8), spironolactone group 21 (1.6)
Interventions	**Intervention** • Flutamide 250 mg b.i.d. + triphasic OCP for 9 months (28) **Comparator** • Spironolactone 50 mg b.i.d. + triphasic OCP for 9 months (27) No epilatory technique was allowed during the study
Outcomes	Assessments (10): baseline and then monthly **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Acne score, seborrhoea and hair loss (Cremoncini 1976) * 3. Serum gonadotropins, prolactin, SHBG, and steroid levels * 4. Biochemical, haematologic, hepatic and renal function 5. Side effects * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 282): "...were randomized into two groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Cusan 1994 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/53 (9%); 1/28 flutamide group, 4/27 spironolactone group, reasons unreported Comment: low number of drop-outs and although not entirely balanced, we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 281): "Supported in part by Schering-Plough". Schering-Plough is the manufacturer of flutamide Moderate baseline imbalance in hirsutism score (25 (1.8) for flutamide group and 21 (1.6) for spironolactone group) Comment: unclear to what extent both of these factors represent a potential risk of bias

De Leo 2000

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, University of Siena, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 35 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute women with PCOS **Exclusion criteria of the trial** • Adrenal or ovarian neoplasm • Congenital or adult adrenal hyperplasia • Cushing's syndrome • Drug-induced hirsutism Randomised N = 35 Withdrawals/losses to follow-up

	• No losses to follow-up reported Baseline data (mean (SD)) BMI: GnRH-a group 22 (2), GnRH-a+OCP group 20 (1.5), GnRH-a+flutamide group 21 (1) Menses, oligomenorrhoea/amenorrhoea: GnRH-a group 7/8, GnRH-a+OCP group 8/4, GnRH-a+flutamide group 6/5 F-G score: GnRH-a group 18 (3), GnRH-a+OCP group 19 (2), GnRH-a+flutamide group 20 (4)
Interventions	**Intervention** • GnRH analogue (triptorelin) 3.75 mg every 28 days for 6 months (12) **Comparator 1** • GnRH analogue (triptorelin) 3.75 mg every 28 days + OCP (cyproterone acetate 2 mg/EE 0.035 mg) for 6 months (12) **Comparator 2** • GnRH analogue (triptorelin) 3.75 mg every 28 days + flutamide 250 mg once a day for 6 months (11)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum LH, FSH, SHBG, estradiol, estrone, total testosterone, free testosterone, androstenedione and DHEAS * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 412-3): "...randomly divided on the basis of a random number table... " and "The obese patients were randomly assigned to group A (n=4), group B (n=4) and group C (n=4)" Comment: it is unclear if a stratified randomisation has been applied for the obese participants and thus if sequence generation has been generated at random E-mail correspondence: did not provide additional information to permit altering the assessment
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been fore-

De Leo 2000 (*Continued*)

		seen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Dereli 2005

Methods	Randomised, open-label, active-controlled trial Setting Department of Endocrinology and Metabolism, Ege University, Izmir, Turkey Date of study Not reported. Duration of intervention 8 months
Participants	N = 264 screened, 40 randomised Mean age = 30 years **Inclusion criteria of the trial** • PCOS based on: hyperandrogenism and/or hyperandrogenaemia, oligo-anovulation, exclusion of other known disorders, such as Cushing's syndrome, hyperprolactinaemia, nonclassic adrenal hyperplasia • BMI < 27 kg/cm^2 • Impaired glucose tolerance test • HOMA > 2.7 **Exclusion criteria of the trial** • BMI > 27 kg/cm^2 • Unresolved medical conditions • Type I or II diabetes mellitus

	• Significant cardiovascular disease, active cancer within the past 5 years • Medications known to affect reproductive or metabolic functions < 60 days prior to study entry Randomised N = 40 Withdrawals/losses to follow-up • 4/40 (10%); 2/20 in rosiglitazone 2 mg group, 2/20 in rosiglitazone 4 mg group • Moved away; 0/20 in rosiglitazone 2 mg group, 1/20 in rosiglitazone 4 mg group • Desire for pregnancy; 1/20 in rosiglitazone 2 mg group, 1/20 in rosiglitazone 4 mg group • Unknown reason; 1/20 in rosiglitazone 2 mg group, 0/20 in rosiglitazone 4 mg group Baseline data (mean (SD)) BMI: rosiglitazone 2 mg group 23.9 (1.9), rosiglitazone 4 mg group 31.4 (0.9) F-G score: rosiglitazone 2 mg group 14.1 (3.8), rosiglitazone 4 mg group 14.2 (4.1) Free testosterone (pg/ml): rosiglitazone 2 mg group 5.69 (1.1), rosiglitazone 4 mg group 5.73 (1.2) Ovulation: rosiglitazone 2 mg group 0, rosiglitazone 4 mg group 0
Interventions	**Intervention** • Rosiglitazone 2 mg once a day for 8 months (20) **Comparator** • Rosiglitazone 4 mg once a day for 8 months (20)
Outcomes	Assessments (3): baseline, month 3 and 8 **Outcomes of the trial** (as reported) 1. Ovulatory function * 2. Ferriman-Gallwey score * 3. Serum total testosterone, free testosterone, estradiol, estrone, androstenedione, LH, FH, 17OH progesterone, DHEAS, prolactin * 4. Glycaemic parameters (fasting and post challenge levels of glucose and insulin, HOMA-IR, haemoglobin A1c) * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 300): "Patients entering the trial received a code provided by a computer program generating random numbers at trial centre..." Comment: probably done

Dereli 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 301): "open labeled trial..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 301): "open labeled trial..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/40, reasons reported. Per-protocol analysis Comment: low and balanced number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	High risk	Although the authors conducted clinical, hormonal, and glycaemic evaluations the following outcomes were either not reported or inadequately reported: evaluation of levels of testosterone, androstenedione, DHEAS, and 17OH progesterone Comment: we judged this as at a high risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Dixon 1991

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynaecology and of Endocrinology, Guy's Hospital, London, UK Date of study Not reported. Duration of intervention 6 months
Participants	N = 41 Mean age = 26 years **Inclusion criteria of the trial**

	• Hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 41 Withdrawals/losses to follow-up • 8/41 (20%); 3/21 in spironolactone group, 5/20 in CPA group reasons not reported Baseline data (mean (SEM)) Testosterone (nmol/L): spironolactone group 2.9 (0.2), CPA group 2.7 (0.2) SHBG (nmol/L): spironolactone group 29.8 (2.8), CPA group 33.6 (3.2) Hair growth (mm/day): spironolactone group 0.38 (0.03), CPA group 0.37 (0.02) F-G score: spironolactone group 23.0 (1.3), CPA group 20.5 (1.3)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + norethisterone 500 µg) + spironolactone 50 mg b.i.d. for 6 months (21) **Comparator** • Ethinyl estradiol 30 µg on days 5 to 25 + cyproterone acetate 50 mg a day on days 5 to 15 (20)
Outcomes	Assessments (3): baseline, month 2 and 6 **Outcomes of the trial** (as reported) 1. Photographic assessment (2 methods) of hirsutism * 2. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review
Notes	1 participant included did not have PCOS or idiopathic hirsutism but delayed onset congenital adrenal hyperplasia (in the spironolactone group). Although this single participant did not match the inclusion criteria we consider this to be of limited impact on the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 64): "...allocated at random..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 64): "... allocated at random by envelope to treatment..." Comment: the report provides sufficient

Dixon 1991 (*Continued*)

		detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 64): "The photographs were coded and all calculations for linear hair growth rate made at the completion of the 6 months. Thus the results were not known by patients or observer during the trial" Comment: although the blinding of the outcome assessment with respect to the photographical assessment might have been adequate, as there was no blinding for treatment arm, the assessment of Ferriman-Gallwey score is likely to be influenced by lack of blinding. With respect to all outcome assessments, we have judged this domain as unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	8/41 (20%); 3/21 in spironolactone group, 5/20 in CPA group reasons not reported. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Eisenhardt 2006

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Gynecological Endocrinology and Reproductive Medicine of the Women's University Hospital Heidelberg, Heidelberg, Germany Date of study 2002 until 2004. Duration of intervention 12 weeks
Participants	N = 45 Mean age = 28 years **Inclusion criteria of the trial** • PCOS, based on at least 2 of the 3 following abnormalities: all patients were expected to have disturbed ovulatory function with chronic oligomenorrhoea (cycle length 35 days; less than 9 cycles per year) or amenorrhoea (cycle length 12 weeks) and typical appearance of polycystic ovaries by ultrasound according to the criteria of the Rotterdam consensus meeting 2003 (Rotterdam Criteria PCOS 2004) • Facultatively clinical and/or biochemical signs of hyperandrogenism (serum total testosterone concentration 60 ng/dl or greater (≥ 2.1 nmol/L) or serum androstenedione (A) concentration greater than 2.9 ng/ml (> 10.1 nmol/L)). **Exclusion criteria of the trial** • Impaired glucose tolerance test (fasting glucose 5.6 mmol/L and/or 2-hour glucose 7.8 mmol/L) or any form of diabetes mellitus • Hyperprolactinaemia • Thyroid disorders • Late onset congenital adrenal hyperplasia (exclusion of 21-hydroxylase deficiency by molecular genetic analysis) • Cushing's syndrome (normal basal free serum cortisone and 2 mg dexamethasone suppression test) • Medications likely to influence hormonal profiles or anti obesity compounds during 6 months before inclusion in the study • Heart, liver, or kidney diseases (predisposing lactic acidosis) and unsuspected pregnancy before inclusion in the study Randomised N = 45 Withdrawals/losses to follow-up • 7/45 (16%); 3/22 in metformin group, 4/23 in placebo group • Socio-economic reasons; 1/22 in metformin group, 3/23 in placebo group • Pregnancy; 2/22 in metformin group, 1/23 in placebo group Baseline data (median (1 to 3 quartiles)) BMI: metformin group 28.9 (23.3 to 34.1), placebo group 32.4 (27.9 to 37.5) F-G score: metformin group 10.1 (8.5 to 12.3), placebo group 9.3 (7.8 to 11.2)
Interventions	**Intervention** • Metformin, first week 500 mg b.i.d. thereafter 500 mg 3 times a day for 12 weeks (22) **Comparator** • Placebo for 12 weeks (23) Participants were advised to use barrier contraception if fertility was not desired and were carefully instructed to stop taking the drug immediately on confirmation of pregnancy

Outcomes	Assessments (4): baseline, month 1, 2, and 3 **Outcomes of the trial** (as reported) 1. Menstrual cycle frequency, basal body temperature curve * 2. Height, weight, BMI * 3. Ferriman-Gallwey score * 4. Serum prolactin, LH, FSH, estradiol, total testosterone, SHBG, progesterone, TSH, total T3, free T4, DHEAS, androstenedione, 17OH- progesterone, cortisol, fasting glucose and insulin, total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol * 5. Complete blood count, hepatic function tests and renal chemistry *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 947): "Randomization was done in a prospective, placebo-controlled, double-blind fashion stratified for insulin resistance. Patients received either metformin or placebo according to computer-generated code with a randomization in blocks of six." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 947): "A copy of the code was stored in a sealed envelope by a third party who did not participate in the study for emergency situations. The randomization code was not broken until the last patient completed all observations." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 947): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind personnel from knowledge of which intervention a participant received,

Eisenhardt 2006 (*Continued*)

		to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 947): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/45 (16%); 4/22 in metformin group, 3/23 in placebo group. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 951): "We are indebted to Merck (Darmstadt, Germany) and Lipha S.A. (Pharmacie Centrale (Clinical Trial Supply Group), Meyzieu, France) for the unconditional supply of metformin and placebo." Comment: we judged this as at a low risk of bias

Elkind-Hirsch 1995

Methods	Randomised, active-controlled trial Setting Baylor College of Medicine, and Obstetrical and Gynecological Associates, Houston, Texas, US Date of study Not reported. Duration of intervention 6 months
Participants	N = 36 recruited Mean age = 28 years **Inclusion criteria of the trial** • Hirsutism (Lorenzo score) (Lorenzo 1970) • Clinical and biochemical criteria for ovarian hyperandrogenism • Testosterone ≥ 60 but ≤ 200 ng/dl, prolactin ≥ 20ng/ml, DHEAS ≤ 320 µg/dl, estradiol ≥ 60 pg/ml, and LH:FSH ratio ≥ 2 **Exclusion criteria of the trial**

	• Smoking < 5 years prior to study entry • Hyperandrogenism due to adrenal or ovary tumours • Cushing's disease • 21-hydroxylase deficiency • Thyroid dysfunction • Elevated DHEAS • Hyperprolactinaemia • OCP, spironolactone, GnRH analogues < 6 months prior to study entry • Medication known to affect gonadotropins, steroid metabolism, or hair growth Randomised N = 36 Withdrawals/losses to follow-up • 3/36 (8%); 0/12 in GnRH-a group, 2/12 in OCP group, 1/12 in GnRH-a +OCP group • Intolerance to OCP; 2/12 in OCP group Baseline data (mean (SEM)) BMI: GnRH-a group 40 (2.0), GnRH-a + OCP group 35.0 (3.0), OCP group 32.0 (2.3) Testosterone (ng/dl): GnRH-a group 79.3 (5.6), GnRH-a + OCP group 91.0 (5.7), OCP group 71.0 (3.8) Free testosterone (ng/dl): GnRH-a group 3.5 (0.4), GnRH-a + OCP group 4.8 (0.6), OCP group 3.1 (0.2) SHBG (nmol/L): GnRH-a group 48 (7), GnRH-a + OCP group 47 (6), OCP group 68 (15) Hirsutism score (Lorenzo 1970): GnRH-a group 15.0 (1.1), GnRH-a + OCP group 16.0 (1.0), OCP group 12.7 (0.8)
Interventions	**Intervention** • GnRH analogue (leuprolide) 3.75 mg im every 28 days for 6 months (12) **Comparator 1** • OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg) for 6 months (12) **Comparator 2** • GnRH analogue (leuprolide) 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg) for 6 months (12)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Serum testosterone, free testosterone, estradiol, DHEAS, progesterone, LH, FSH, SHBG, insulin * 2. Hirsutism (modified Lorenzo score) (Lorenzo 1970) * 3. Hair shaft diameter * 4. Hair density * 5. Transvaginal ultrasound examination 6. Adverse events *

Elkind-Hirsch 1995 (*Continued*)

	7. Frequency of performing cosmetic measures (by participants) 8. Participant self report * *Denotes outcomes prespecified for this review
Notes	30/36 were obese having BMI > 29 kg/m^2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 971): "... were assigned randomly..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported. However, hair shaft diameter and density was assessed by a dermatologist who was blinded as well as the ultrasound scans were performed by a blinded investigator Comment: although the objective measurement of the hirsutism and ultrasound scans might have been assessed by a blinded investigator, the assessment of the other outcomes were not blinded. The outcome measurement of most outcomes was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/36 (8%); 0/12 in GnRH-a group, 2/12 in OCP group, 1/12 in GnRH-a +OCP group. Per-protocol-analysis Comment: low number of drop-outs at follow-up and, although per-protocol analy-

Elkind-Hirsch 1995 (*Continued*)

		sis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 970 and 977): "Supported by an educational grant from TAP Pharmaceuticals, Deerfield, Illinois and by the division of Research resources of the National Institutes of Health under grant MO1RR00350, Bethesda, Maryland" and "We express our thanks...to TAP Pharmaceuticals in Deerfield, Illinois and Mead Johnson Laboratories in Evansville Indiana for their generous gifts of Lupron and Ovcon-35." There was serious baseline imbalance in BMI between the groups Comment: a potential risk of bias cannot be excluded

Elnashar 2006

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, Benha University Hospital, Benha, Egypt Date of study March until December 2004. Duration of intervention 1 treatment cycle
Participants	N = 80 Mean age = 24 years **Inclusion criteria of the trial** • Infertile women with PCOS according to the Rotterdam criteria (Rotterdam Criteria PCOS 2004) • 18 and 39 years • Period of infertility > 2 years • DHEAS within normal levels (80 to 400 μg/dl) • Previously received clomiphene citrate (CC) and diagnosed as having CC resistance (failure of ovulation after 3 cycles of CC reaching the dose of 150 mg daily) **Exclusion criteria of the trial** • Hyperprolactinaemia, clinical evidence of hypercorticism or thyroid dysfunction • Treatment last 2 months prior to the dexamethasone treatment Randomised N = 80 Withdrawals/losses to follow-up

	• No losses to follow-up reported Baseline data (mean (SD)) BMI: CC + dexamethasone group 29.381 (5.1195), CC group + placebo 29.595 (5.7958) Waist/hip ratio: CC + dexamethasone group 0.8948 (0.0940), CC group + placebo 0.9627 (0.0851) Oligomenorrhoea/amenorrhoea: CC + dexamethasone group 31/40, CC group + placebo 32/40 Eumenorrhoea: CC + dexamethasone group 9/40, CC group + placebo 8/40 Hirsutism: CC + dexamethasone group 11/40, CC group + placebo 13/40
Interventions	**Intervention** • Clomiphene citrate 100 mg/day on day 3 to 7 + dexamethasone 2 mg/day on day 3 to 12 (40) **Comparator** • Clomiphene citrate 100 mg/day on day 3 to 7 + placebo on day 3 to 12 (40)
Outcomes	Assessments (2); baseline and end of cycle **Outcomes of the trial** (as reported) 1. Ovulation rate * 2. Number of follicles of > 18 mm endometrial thickness and pregnancy rate *Denotes outcomes prespecified for this review
Notes	No separate data reported for participants with hirsutism, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 1806): "Patients were assigned randomly to receive CC and either DEX or placebo using closed dark envelopes" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 1806): "Patients were assigned randomly to receive CC and either DEX or placebo using closed dark envelopes" Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done

Elnashar 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1806): "The patient and the physician monitoring the cycles were blinded to the identity of each medication" Comment: the report did not provide sufficient detail about the specific measures used to blind personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1806): "The patient and the physician monitoring the cycles were blinded to the identity of each medication" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Elter 2002

Methods	Randomised, active-controlled trial Setting Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Marmara University School of Medicine, Istanbul, Turkey Date of study Not reported. Duration of intervention 4 months
Participants	N = 40 Mean age = 24 years **Inclusion criteria of the trial** • PCOS based on (i) bilateral polycystic ovaries on ultrasound examination, (ii) chronic oligo-menorrhoea (< 6 menstrual periods in previous year), (iii) manifestations of hyperandrogenism and/or hyperandrogenaemia, i.e. hirsutism score > 8 (Ferriman-

	Gallwey score), acne, elevated serum testosterone and/or androstenedione and/or free testosterone levels • BMI ≤ 26 kg/m^2 **Exclusion criteria of the trial** • Late-onset congenital adrenal hyperplasia • Serum 17OH progesterone > 10 nmol/L after ACTH stimulation • Serum cortisol > 140 nmol/L after dexamethasone suppression test • Adrenal mass on pelvic sonography • Diabetes • Endocrinological disease • Drugs that affect carbohydrate or lipid metabolism and OGTT results < 6 months prior to study entry Randomised N = 40 Withdrawals/losses to follow-up • No drop-outs Baseline data (mean (SD)) BMI: OCP + metformin group 22.74 (2.66), OCP group 21.83 (1.40) Waist/hip ratio: OCP + metformin group 0.827 (0.06), OCP group 0.804 (0.04) F-G score: OCP + metformin group 9.47 (5.48), OCP group 12.06 (5.25) (14 in each group were hirsute) Testosterone (nmol/L): OCP + metformin group 2.72 (1.21), OCP group 2.76 (1.61) Free testosterone (pg/ml): OCP + metformin group 13.10 (3.11), OCP group 13.00 (4.62) Androstenedione (nmol/L): OCP + metformin group 10.65 (3.53), OCP group 10.87 (2.53) DHEAS (µmol/L): OCP + metformin group 6.31 (2.30), OCP group 7.69 (3.21) SHBG (nmol/L): OCP + metformin group 54.99 (22.27), OCP group 52.97 (19.08)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + metformin 500 mg 3 times a day for first 15 days then b.i.d. for 4 months (20) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) (20)
Outcomes	Assessments (2): baseline and month 4 **Outcomes of the trial** (as reported) 1. BMI, waist/hip ratio * 2. Ferriman-Gallwey score * 3. Ovary volume 4. Serum FSH, LH, testosterone, free testosterone, androstenedione, DHEAS, SHBG, 17OH progesterone * 5. Glucose, insulin, total cholesterol, LDL cholesterol, HDL cholesterol * Denotes outcomes prespecified for this review
Notes	14 in each group were hirsute

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 1730): "Randomization was produced from a computer-generated random list..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1730): "Clinical parameters (BMI, WHR, Ferriman-Gallwey score and ovarian volume) of the subjects were evaluated by the same person, who was blind to the type of treatment. No attempt was made to mask the treatments from the subjects, and placebo was not used" Comment: we judged this as at unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1730): "Clinical parameters (BMI, WHR, Ferriman-Gallwey score and ovarian volume) of the subjects were evaluated by the same person, who was blind to the type of treatment. No attempt was made to mask the treatments from the subjects, and placebo was not used" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk

		of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Erenus 1994

Methods	Randomised, active-controlled trial Setting Marmara University Hospital Hirsutism Clinic, Istanbul, Turkey Date of study Not reported. Duration of intervention 9 months
Participants	N = 20 Mean age = 20 years **Inclusion criteria of the trial** • Idiopathic hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 20 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: flutamide group 23.1 (3.75), spironolactone group 22.5 (3.5) F-G score: flutamide group 21.2 (6), spironolactone group 19.8 (5.6) Testosterone (ng/dl): flutamide group 41.39 (17.5), spironolactone group 49.4 (10.3) DHEAS (mg/dl): flutamide group 178.8 (84.64), spironolactone group 218.4 (142.5)
Interventions	**Intervention** • Flutamide 250 mg b.i.d. for 9 months (10) **Comparator** • Spironolactone 100 mg/day for 9 months (10)
Outcomes	Assessments (4): baseline, month 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum testosterone, DHEAS, FSH, LH * 3. Adverse effects * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Erenus 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 614): "... were randomized to receive..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Erenus 1996

Methods	Randomised, single-blind, active-controlled trial Setting Marmara University School of Medicine, Istanbul, Turkey Date of study Not reported. Duration of intervention 9 months
Participants	N = 42 Mean age = 21 years **Inclusion criteria of the trial** • Hirsutism (Ferriman-Gallwey score > 10) **Exclusion criteria of the trial** • Medication < 6 months before study entry Randomised N = 42 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) F-G score: CPA group 18.28 (4.60), spironolactone group 18.04 (5.90) Testosterone (ng/dl): CPA group 48.5 (22.20), spironolactone group 46.31 (24.92) DHEAS (mg/dl): CPA group 275.4 (103.0), spironolactone group 276.26 (103.28)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + 50 mg cyproterone acetate on days 1 to 10 for 9 months (21) **Comparator** • OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) + 100 mg spironolactone/day for 9 months (21)
Outcomes	Assessments (4): baseline, month 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum testosterone, DHEAS, FHSH, LH, and 17OH progesterone * 3. Adverse events * * Denotes outcomes prespecified for this review
Notes	3 participants had PCOS, 37 idiopathic hirsutism, and 2 had late onset adrenal hyperplasia. Although these last 2 participants did not match the inclusion criteria we consider this to be of limited impact on the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 217): "... were randomly assigned in a 1:2 ratio..." Comment: insufficient detail was reported

		about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 216): "...single-blinded..." Comment: the report did not provide sufficient detail about the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 217): "Measurements were performed by a single examiner (D.Y.) who was blinded with regard to treatment." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Erenus 1997

Methods	Randomised, single-blind, active-controlled trial Setting Marmara University School of Medicine, Istanbul, Turkey Date of study Not reported. Duration of intervention 9 months
Participants	N = 40 Mean age = 20 years **Inclusion criteria of the trial** • Idiopathic hirsutism (Ferriman-Gallwey score > 10) **Exclusion criteria of the trial** • Medication < 6 months before study entry Randomised N = 40 Withdrawals/losses to follow-up • 24/40 (60%); 13/20 in finasteride group, 11/20 in spironolactone group • Inefficacy of treatment; 13/20 in finasteride group, 6/20 in spironolactone group • Additional OCP because of irregular bleeding; 5/20 in spironolactone group Baseline data (mean (SD)) F-G score: finasteride group 20.05 (5.01), spironolactone group 21.60 (5.56) Testosterone (ng/dl): finasteride group 41.67 (14.82), spironolactone group 48.49 (17.40) DHEAS (mg/dl): finasteride group 224.71 (82.19), spironolactone group 244.30 (121.78)
Interventions	**Intervention** • Finasteride 5 mg/day for 9 months (20) **Comparator** • Spironolactone 100 mg/day for 9 months (20)
Outcomes	Assessments (4): baseline, month 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum testosterone, DHEAS, FHSH, LH and 17OH progesterone * 3. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1001): "... were randomly assigned in a 1:1 ratio..." Comment: insufficient detail was reported

		about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1000): "...single-blinded..." Comment: the report did not provide sufficient detail about the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1001): "Measurements were performed by a single examiner (D.Y.) who was blinded with regard to treatment" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	24/40 (60%); 13/20 finasteride group, 11/20 in spironolactone group at the end of the study. Per-protocol-analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Erkkola 1990

Methods	Randomised, open, active-controlled trial Setting Multi-centre (5) in Finland Date of study Not reported. Duration of intervention 9 months
Participants	N = 162 Age range = 20 to 40 years **Inclusion criteria of the trial** • Desire for oral contraception • Androgenisation symptoms (acne, seborrhoea, and hirsutism) **Exclusion criteria of the trial** • Not reported Randomised N = 162 Withdrawals/losses to follow-up • 29/162 (18%); 14/83 cyproterone acetate + ethinyl estradiol group, 15/79 desogestrel + ethinyl estradiol group • Irregular bleeding; 1/83 cyproterone acetate + ethinyl estradiol group, 5/79 desogestrel + ethinyl estradiol group • Other side effects such as headache, reduced libido, breast tenderness, nervousness, depression, oedema; 13/83 cyproterone acetate + ethinyl estradiol group, 10/79 desogestrel + ethinyl estradiol group Baseline data Hirsutism: CPA + EE group 3/83, desogestrel + EE group 6/79
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 9 months (83) **Comparator** • OCP (ethinyl estradiol 30 μg+ desogestrel 0.15 mg) for 9 months (79)
Outcomes	Assessments (4): baseline, month 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Gynaecological examination, including palpation of the mammae 2. Body weight and blood pressure 3. Bleeding patterns 4. Side effects * 5. Assessments of acne, greasy skin, and hirsutism; 3-point Likert scale * *Denotes outcomes prespecified for this review
Notes	No separate data reported for participants with hirsutism, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 62):"... randomly enrolled into the study..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 61): "...open, randomized..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 61): "...open, randomized..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	29/162 (18%); 14/83 cyproterone acetate + ethinyl estradiol group, 15/79 desogestrel + ethinyl estradiol group. Per-protocol-analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	High risk	Outcomes for hirsutism were prespecified in the 'methods' and evaluated, but were not reported Comment: we judged this as at a high risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Esmaeilzadeh 2010

Methods	Randomised, double-blind, active-controlled trial Setting Department of Infertility and Reproductive Health Research Center, Babol University of Medical Sciences, Babol, Iran Date of study Not reported. Duration of intervention 6 months
Participants	N = 40 Age range = 18 to 45 years **Inclusion criteria of the trial** • Obese women with PCOS according to the Rotterdam criteria (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Ovarian or adrenal tumours • Congenital adrenal hyperplasia • Ovarian hypertrophy • Cushing's syndrome • Hyperprolactinaemia • Use of progesterone/danazol medications • Thyroid abnormalities • Pregnant women • On medication with a diet < 3 months prior to study entry Randomised N = 40 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: metformin group 33.7 (4.72), flutamide group 31.8 (3.99) Waist/hip ratio: metformin group 0.82 (0.05), flutamide group 84 (0.05) F-G score: metformin group 10.5 (3.6), flutamide group 9.4 (2.52) Total testosterone (nmol/L): metformin group 1.02 (0.63), flutamide group 0.81 (0.47) Free testosterone (pmol/L): metformin group 2.76 (1.72), flutamide group 1.46 (1.42) DHEAS (µmol/L): metformin group 223.12 (103.79), flutamide group 189.49 (186. 98) SHBG (nmol/L): metformin group 26.93 (12.7), flutamide group 26.93 (12.7)
Interventions	**Intervention** • Metformin 500 mg 3 times a day for 6 months (20) **Comparator** • Flutamide 250 mg b.i.d. for 6 months (20) Participants started 1 month prior to study entry with a calorie restricted diet (1200 to 1400 kcal/day), which was continued for the duration of the intervention
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Weight, height, BMI, waist circumference, waist/hip ratio * 2. Ferriman-Gallwey score * 3. Serum testosterone, free testosterone, DHEAS, SHBG

	* 4. Glucose, insulin, OGTT, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	From the translation: were randomly chosen (method unspecified) Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (English abstract): "...double-blind. .." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (English abstract): "...double-blind. .." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Falsetti 1992

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynaecology and Department of Pathology, University of Brescia, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 20 Mean age = not reported **Inclusion criteria of the trial** • Idiopathic hirsutism (10), hirsutism in women with PCOS (10) **Exclusion criteria of the trial** • Not reported Randomised N = 20 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) F-G score: idiopathic hirsutism 17 (5), hirsutism in PCOS 16 (4)
Interventions	**Intervention** • Leuprorelin 3.75 mg im every 28 days for 6 months (10) **Comparator** • Leuprorelin 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 6 months (10)
Outcomes	Assessments: (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum testosterone, free testosterone, androstenedione, DHEAS, SHBG, 17OH progesterone, insulin, LH, FSH * *Denotes outcomes prespecified for this review
Notes	Letter to the Editor, limited information

Falsetti 1992 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 894): "... we randomized..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome assessment was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Falsetti 1994

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynaecology and Department of Pathology, University of Brescia, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 32 Mean age = 25 years **Inclusion criteria of the trial** • Moderate to severe hirsutism (Ferriman-Gallwey score 11 to 25) • Idiopathic hirsutism (16), hirsutism in PCOS (16) **Exclusion criteria of the trial** • Not reported Randomised N = 32 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) F-G score: idiopathic hirsutism 15.3 (4.0), hirsutism in PCOS 17.5 (4.4) Regular cycles: idiopathic hirsutism 12/16, hirsutism in PCOS 0/16 Oligomenorrhoea: idiopathic hirsutism 4/16, hirsutism in PCOS 16/16 Testosterone (ng/ml): idiopathic hirsutism 0.6 (0.1), hirsutism in PCOS 1.4 (0.4) Free testosterone (pg/ml): idiopathic hirsutism 2.0 (0.6), hirsutism in PCOS 5.1 (2.1) Androstenedione (ng/ml): idiopathic hirsutism 3.3 (0.4), hirsutism in PCOS 2.1 (0.3) DHEAS (μg/ml): idiopathic hirsutism 1.6 (0.8), hirsutism in PCOS 2.1 (0.7) SHBG (nmol/L): idiopathic hirsutism 44.7 (6.3), hirsutism in PCOS 16.3 (0.2)
Interventions	**Intervention** • Leuprolide 3.75 mg im every 28 days for 6 months (16) **Comparator** • Leuprolide 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 6 months (16)
Outcomes	Assessments: (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Hair diameter * 3. Serum testosterone, free testosterone, androstenedione, DHEAS, SHBG, 17OH progesterone, estradiol, insulin, LH, FSH * 4. Ovarian morphology (ultrasound) 5. Bone density measurement *Denotes outcomes prespecified for this review
Notes	-

Falsetti 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 817/8): "randomly allocated.. . two randomized treatment arms were created..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome assessment was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Falsetti 1994B

Methods	Randomised, active-controlled trial Setting Department of Gynaecological Endocrinology, University of Brescia, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 25 Mean age = 24 **Inclusion criteria of the trial** • Moderate severe hirsutism in women with PCOS **Exclusion criteria of the trial** • Not reported Randomised N = 25 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: GnRH-a 22 (3), GnRH-a + OCP 24 (1) Oligomenorrhoea: GnRH-a 12 (100%), GnRH-a + OCP 13 (100%) F-G score: GnRH-a 18 (4), GnRH-a + OCP 17 (3) Androstenedione (ng/ml): GnRH-a 3.4 (0.2), GnRH-a + OCP 3.5 (0.3) Testosterone (ng/ml): GnRH-a 1.2 (0.3), GnRH-a + OCP 1.5 (0.4) Free testosterone (pg/ml): GnRH-a 5.0 (0.4), GnRH-a + OCP 5.2 (0.9) DHEAS (μg/ml): GnRH-a 2.1 (0.5), GnRH-a + OCP 2.0 (0.3) SHBG (nmol/L): GnRH-a 15.0 (7.0), GnRH-a + OCP 17.0 (6.0)
Interventions	**Intervention** • Leuprolide 3.75 mg im every 28 days for 6 months (12) **Comparator** • Leuprolide 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 6 months (13)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Hair diameter * 3. Serum testosterone, free testosterone, androstenedione, DHEAS, SHBG, 17OH progesterone, insulin, insulin growth factor 1, LH, FSH * 4. Ovarian morphology (ultrasound) 5. Bone density measurement 6. Side effects * * Denotes outcomes prespecified for this review
Notes	-

Falsetti 1994B (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 304): "The randomization created two different groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome assessment was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Falsetti 1999

Methods	Randomised, active-controlled trial Setting Department of Gynaecological Endocrinology, University of Brescia, Italy Date of study Not reported. Duration of intervention 12 months
Participants	N = 110 Mean age = 23 years **Inclusion criteria of the trial** • Hirsute women with PCOS (64) or idiopathic hirsutism (46) • Diagnosis of PCOS was based on clinical and endocrine findings **Exclusion criteria of the trial** • Cushing's syndrome • Evidence of enzymatic adrenal deficiency • History of drug-induced hyperandrogenism • Endocrine profile compatible with androgen-producing neoplasm or prolactin and thyroid disorder Randomised N = 110 Withdrawals/losses to follow-up • 3/110 (3%); 0/55 in finasteride group, 3/55 in flutamide group • High transaminase; 2/55 in flutamide group • Nausea and vomiting; 1/55 in flutamide group Baseline data (mean (SD)) BMI: PCOS group 23.7 (4.1), idiopathic hirsutism 22.4 (3.2) Androstenedione (ng/ml): PCOS group 3.6 (0.6), idiopathic hirsutism 2.0 (0.4) Testosterone (ng/ml): PCOS group 1.0 (0.2), idiopathic hirsutism 0.5 (0.1) Free testosterone (pg/ml): PCOS group 3.4 (0.6), idiopathic hirsutism 1.9 (0.6) DHEAS (μg/ml): PCOS group 2.8 (0.9), idiopathic hirsutism 2.1 (0.8) SHBG (nmol/L): PCOS group 22.0 (6.2), idiopathic hirsutism 46.0 (6.5)
Interventions	**Intervention** • Finasteride 5 mg daily for 12 months (55) **Comparator** • Flutamide 250 mg b.i.d. for 12 months (55)
Outcomes	**Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Hair diameter (4 different body areas) * 3. Serum testosterone, free testosterone, androstenedione, DHEAS, SHBG, 17OH progesterone, insulin, 3α-diol G, LH, FSH * 4. Haematochemical examinations (haemochrome, glycaemia, azotaemia, creatinaemia, electrophoretic protidogram, total and fractioned bilirubinaemia, alkaline phosphatase, transaminases) 5. Menstrual cycle *

	6. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 362): "...were randomly assigned in 1:1 ratio..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome assessment was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/110 (3%); 0/55 in finasteride group, 3/55 in flutamide group, reasons reported. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Falsetti 1999 (*Continued*)

Other bias	Low risk	The study appears to be free of other forms of bias

Farina 2006

Methods	Two randomised, active-controlled studies Setting Microbiological and Gynecological Science Department, Gynecology Section Santo Bambino" Hospital, University of Catania, Italy Date of study Not reported. Duration of intervention 12 months
Participants	N = 60 in study A, N = 60 in study B Mean age = 24 years in study A, 25 years in study B **Inclusion criteria of the trial** • Normal cervical smear, not pregnant • Euthyroid, spontaneous onset of puberty and sexual development • Normal renal and hepatic functions, lipids and hormonal evaluation (serum tests) • Normal gynaecological and dermatological (acne seborrhoea and hirsutism) screening **Exclusion criteria of the trial** • Contraindication for OCP • Hormonal treatment, or drugs known to affect plasma sex steroid concentration < 3 months prior to study entry • Isotretinoin, systemic antibiotics, or other systemic or topical acne treatments (< 6, 4, and 2 weeks prior to study entry respectively) Randomised N = 60 in study A, N = 60 in study B Withdrawals/losses to follow-up • 19/60 (32%) study A; 8/30 DRSP + EE group, 11/30 DSG + EE group i) Adverse events: 4/30 DRSP + EE group (2 headache, 1 breast tenderness, 1 amenorrhoea), 8/30 DSG + EE group (5 headache, 2 cellulitis, 1 nausea and vomiting) ii) Non-compliance: 4/30 DRSP + EE group, 3/30 DSG + EE group • 21/30 (35%) study B; 10/30 DRSP + EE group, 11/30 DSG + EE group i) Adverse events: 3/30 DRSP + EE group (2 headache, 1 nausea), 6/30 DSG + EE group (3 headache, 2 amenorrhoea, 1 cellulitis) ii) Non-compliance: 7/30 DRSP + EE group, 5/30 DSG + EE group Baseline data Not reported. Only figures are provided
Interventions	**Study A** **Intervention** • OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) for 12 months (30) **Comparator** • OCP (ethinyl estradiol 40 to 30 μg + desogestrel 25 to 125 μg) for 12 months (30) **Study B** **Intervention**

	• OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) for 12 months (30) **Comparator** • OCP (ethinyl estradiol 20 μg + desogestrel 0.15 mg) for 12 months (30)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey scores * 2. Acne and seborrhoea (Cremoncini 1976) * 3. Haematological and hormonal evaluations * 4. Gynaecological evaluation 5. Menstrual cycles * 6. Adverse events * * Denotes outcomes prespecified for this review
Notes	Inconsistent and incomplete reporting of outcomes data across intervention groups. No reliable or usable data. See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 20): "... randomizzati...". Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding

Farina 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	High drop-out rate (32% in study A, 35% in study B). Intention-to treat analysis (last observation carried forward) Comment: although an intention-to treat analysis was used, the high drop-out rate represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Farquhar 2002

Methods	Randomised, active-controlled trial Setting Tertiary level fertility clinics in Auckland, New Zealand Date of study Between mid 1996 and late 1999. Duration of study 6 months
Participants	N = 50 Mean age = 30 years **Inclusion criteria of the trial** • 20 to 38 years with PCOS • Clomiphene citrate resistance (no ovulation after one or more cycles of 150 mg of clomiphene citrate from day 2 to day 6 each month), infertility of 12 months duration, polycystic ovaries on ultrasound scan, a body mass index of 33 kg/m^2 for women of European descent and of 35 kg/m^2 for women of Pacific Island or NZ Maori descent, and normal semen analysis (20 million per millilitre, 96% abnormal forms, and 50% motility) **Exclusion criteria of the trial** • Other known causes of infertility, including male factor infertility or known tubal disease Randomised N = 50 Withdrawals/losses to follow-up • 3/50 (6%); 1/29 in laparoscopic ovarian diathermy group, 2/21 in gonadotropins group Baseline data (mean (SD)) BMI: laparoscopic ovarian diathermy group 28.3 (3.9), gonadotropins group 27.8 (4.8) F-G score > 8: laparoscopic ovarian diathermy group 15/29, gonadotropins group 10/21 Acne present: laparoscopic ovarian diathermy group 13/29, gonadotropins group 8/21

	Testosterone (nmol/L): laparoscopic ovarian diathermy group 2.1 (0.9), gonadotropins group 2.5 (0.7)
Interventions	**Intervention** • Laparoscopic ovarian diathermy (29) **Comparator** • 3 cycles of urinary gonadotropins (Metrodin HP, Serono, Rome, Italy) or recombinant follicle-stimulating hormone (Puregon, Organon, Oss, The Netherlands or Gonal F, Serono, Rome, Italy) (21)
Outcomes	Assessments (2): baseline and end of study **Outcomes of the trial** (as reported) 1. Ovulation * 2. Pregnancy rates/miscarriage rates * Denotes outcomes prespecified for this review
Notes	No separate data on hirsute women, only one secondary outcome was addressed. See Table 3 Study of Mohiuddin 2007 (second reference under primary reference) is a follow-up study 6 to 10 years later

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 405): "Randomization was performed using computer-generated sequences that were sealed in numbered opaque envelopes" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 405): "...sealed in numbered opaque envelopes" Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding reported Comment: although not blinded, the outcome measurement was not likely to be influenced by the lack of blinding

Farquhar 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	3/50 (6%); 1/29 in laparoscopic ovarian diathermy group, 2/21 in gonadotropins group Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other sources of bias

Fruzzetti 1999

Methods	Randomised, open, active-controlled trial Setting Department of Gynecology and Obstetrics, University of Pisa, Pisa, Italy Date of study Not reported. Duration of intervention 1 year
Participants	N = 45 Mean age = 22 years **Inclusion criteria of the trial** • Hirsutism • Normal prolactin levels **Exclusion criteria of the trial** • Clinical signs of virilisation • Cushing's syndrome • Evidence of enzymatic adrenal deficiency • Drug-induced hyperandrogenism • Markedly elevated plasma androgen levels • History compatible with an androgen-producing neoplasm • Any hormonal treatment in the 6 months prior to study entry Randomised N = 45 Withdrawals/losses to follow-up • 3/45 (7%); 1/15 in finasteride group, 2/15 CPA group, all for personal reasons Baseline data (mean (SE)) BMI: finasteride group 22.80 (1.08), CPA group 26.20 (1.60), flutamide group 21.70 (0.82) F-G score: finasteride group 21.60 (2.47), CPA group 28.40 (1.53), flutamide group 18.00 (1.65) Testosterone (ng/ml): finasteride group 0.59 (0.10), CPA group 0.86 (0.15), flutamide group 0.54 (0.04)

	Androstenedione (ng/ml): finasteride group 3.48 (0.34), CPA group 4.07 (0.45), flutamide group 2.94 (0.28)
Interventions	**Intervention** • Finasteride 5 mg/day for 1 year (15) **Comparator 1** • Cyproterone acetate 25 mg/day, day 1 to 10 of menstrual cycle + ethinyl estradiol 20 μg every day for 21 days for 1 year (15) **Comparator 2** • Flutamide 250 mg b.i.d. (15) Women treated with finasteride and flutamide were advised to use barrier methods of contraception or an intrauterine device during the study to avoid conception of a feminised male fetus
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum LH, FSH, prolactin, P, 17β-E2, total testosterone, free testosterone, androstenedione, DHEAS, dihydrotestosterone, SHBG, and 3α-diol G * 3. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 446): "Women were randomly divided into three treatment groups, with the Ferriman-Gallwey hirsutism score used to stratify women before randomization to prevent differences in hirsutism score among groups." Comment: stratified form of randomisation but insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported

Fruzzetti 1999 (*Continued*)

		Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 445): "...open...study..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 445 and 447): "...open...study..." and "...the physician performing the Ferriman-Gallwey score measures was blinded to the treatment each woman received" Comment: although the assessment of the Ferriman-Gallwey score was blinded, the outcome assessment of the other outcomes was not blinded. We judged this as at unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/45 (7%); 1/15 in finasteride group, 2/15 CPA group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	There was significant baseline imbalance in F-G score between the groups which was not acknowledged in the data analysis Comment: a potential risk of bias cannot be excluded

Fruzzetti 2010

Methods	Randomised, open-label, active-controlled trial Setting Outpatient Clinic of Reproductive Endocrinology of the University of Pisa, Pisa, Italy Date of study March-November 2008 enrolment. Duration of intervention 6 months
Participants	N = 48 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute women with PCOS (Ferriman-Gallwey score > 8)

	• PCOS based on Rotterdam Criteria PCOS 2004 and National Institute of Health criteria (Zawadski 1992) **Exclusion criteria of the trial** • Hypertension • Glucose intolerance or diabetes mellitus • History of cardiovascular events • OCP, antiandrogens, insulin sensitisers, or drugs that might interfere with blood pressure regulation, lipid profile, or carbohydrate metabolism for the previous 6 months • Hyperprolactinaemia • Hypo- or hyperthyroidism • Congenital adrenal hyperplasia • Cushing's syndrome • Androgen-secreting tumours Randomised N = 48 Withdrawals/losses to follow-up • 1/48 (2%); 1/16 DRSP + EE + metformin group due to gastrointestinal side effects Baseline data (mean (SD)) BMI: DRSP + EE group 24.7 (3.0), DRSP + EE + metformin group 24.7 (3.9), DRSP + EE + CPA group 23.8 (2.5) Waist/hip ratio: DRSP + EE group 0.8 (0.2), DRSP + EE + metformin group 0.8 (0.1) , DRSP + EE + CPA group 0.8 (0.1) Testosterone (ng/ml): DRSP + EE group 0.7 (0.3), DRSP + EE + metformin group 0.7 (0.2), DRSP + EE + CPA group 0.8 (0.3) SHBG (ng/ml): DRSP + EE group 29.5 (12.3), DRSP + EE + metformin group 23.7 (10.9), DRSP + EE + CPA group 31.0 (10.3) Androstenedione (ng/ml): DRSP + EE group 3.1 (1.2), DRSP + EE + metformin group 2.5 (0.9), DRSP + EE + CPA group 3.5 (1.0)
Interventions	**Intervention** • OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) for 6 months (16) **Comparator 1** • OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + 500 mg metformin 3 times a day for 6 months (16) **Comparator 2** • OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + cyproterone acetate 12.5 mg (first 10 days of pill strip) for 6 months (16) All patients were instructed to not modify their diet and physical activity throughout the trial
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. BMI * 2. Waist/hip ratio 3. Blood pressure 4. Total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations

	5. Oral glucose tolerance test 6. Plasma samples for glucose and insulin concentrations 7. Total testosterone, androstenedione, and SHBG * 8. AUC-insulin, HOMA-IR, and glucose/insulin ratio * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1794): "The allocation sequence of the treatments was decided by a third party (D.P.) before the recruitment of patients by random-number tables" Comment: probably done
Allocation concealment (selection bias)	High risk	As one of the investigators had access to the random-number table it is likely that allocation could be foreseen Comment: we assessed this as at high risk of bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 1793): "...randomised, open-label clinical trial..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 1793): "...randomised, open-label clinical trial..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/48 (2%); 1/16 DRSP + EE + metformin group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Other bias	Low risk	The study appears to be free of other forms of bias

Gambineri 2005

Methods	Randomised, single-blind, placebo-controlled trial Setting Division of Endocrinology, Department of Internal Medicine, S. Orsola-Malpighi Hospital of Bologna, Bologna, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 20 Mean age = 24 years **Inclusion criteria of the trial** • Overweight or obese women with PCOS • Diagnosis of PCOS made according to the presence of chronic anovulation (supported by luteal progesterone measurement), oligomenorrhoea/amenorrhoea, hirsutism (Ferriman-Gallwey score ≥ 8), or elevations in blood levels of total and free testosterone, and polycystic ovarian morphology at ultrasound **Exclusion criteria of the trial** • Cushing's syndrome • Late-onset congenital adrenal hyperplasia • Hyperprolactinaemia • Thyroid dysfunction • Diabetes • Cardiovascular, renal, or liver disease or gallstones • Significant change in body weight < 3 months prior to study entry • Dieting Randomised N = 20 Withdrawals/losses to follow-up • 2/20 (10%); 2/10 in placebo group because of noncompliance Baseline data (mean (SD)) BMI: octreotide group 35.8 (7.0), placebo group 35.7 (7.5) F-G score: octreotide group 15.0 (6.8), placebo group 7.1 (3.6) Testosterone (ng/ml): octreotide group 0.70 (0.26), placebo group 0.60 (0.18) Androstenedione (ng/dl): octreotide group 335 (66), placebo group 323 (38) DHEAS (µg/ml): octreotide group 2.25 (0.91), placebo group 2.91 (0.47) SHBG (nmol/L): octreotide group 21.5 (13.1), placebo group 20.8 (9.2)
Interventions	**Intervention** • Octreotide-LAR, 10 mg im every month for 6 months (10) **Comparator** • Placebo, saline solution im every months for 6 months (10) Women were placed, for the first month, on a standardised hypocaloric diet (1200 to 1420 kcal/daily). After this period and while continuing dietary treatment, they were randomly placed in the treatment arms

Outcomes	Assessments (3): baseline, month 1 and 7 **Outcomes of the trial** (as reported) 1. Anthropometric parameters (height, weight, waist, and hip circumferences) * 2. Hirsutism (Ferriman-Gallwey score) * 3. Acanthosis nigricans 4. Computerised tomography of body fat distribution 5. Questionnaire of physical activity 6. Frequency of menses * 7. Occurrence of ovulation * 8. Serum glucose, insulin, LH, FSH, testosterone, free testosterone, androstenedione, DHEAS, SHBG, estradiol, progesterone, 17OH progesterone, cortisol and IGF binding proteins * 9. QUICKI, HOMA 10. Adverse events * *Denotes outcomes prespecified for this review
Notes	11/20 participants with PCOS were hirsute (8/10 in octreotide group, 3/10 in placebo group). No separate data on women with hirsutism. See Table 3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 3855): "...in a random order. .." "the random allocation sequence to the two treatments was decided before the recruitment..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	Quote (page 3855: "One investigator (L.P.) generated the random allocation sequence and administered the drugs (active or placebo) at the out-patient clinic for the entire period of the study, whereas another investigator (A.G.),blinded to group assignment, enrolled and regularly checked all patients. "

		The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 3854-5): "...according to a single-blind design...." "whereas another investigator (A.G.), blinded to group assignment, enrolled and regularly checked all patients at monthly intervals" Comment: the report did not provide sufficient detail about the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 3855): "...another investigator enrolled and regularly checked all patients at monthly intervals..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/20 (10%); both in the placebo group because of non-compliance Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 3861): "We are indebted to Novartis Farma S.p.A. (Origgio-Varese, Italy), who provided both octreotide-LAR and octreotide." Baseline imbalance: Ferriman-Gallwey score significantly higher (P value = 0.01) in octreotide than in placebo group Comment: we judged this as at high risk of

Gambineri 2005 (*Continued*)

		bias

Gambineri 2006

Methods	Randomised, single-blind, placebo and active-controlled trial Setting Divisions of Endocrinology and Internal Medicine, Departments of Internal Medicine and Gastroenterology, S. Orsola-Malpighi Hospital, University of Bologna, Italy Date of study Not reported. Duration of intervention 12 months
Participants	N = 80 (40 from previous study (Gambineri 2004) and "extending their treatment") Mean age = 26 years **Inclusion criteria of the trial** • PCOS according to Rotterdam Criteria PCOS 2004 • Reproductive age 18 to 45 years • BMI at least 28 kg/m^2, and waist circumference at least 88 cm, consistent with an abdominal fat distribution phenotype **Exclusion criteria of the trial** • Cushing's syndrome • Late-onset congenital adrenal hyperplasia • Hyperprolactinaemia • Thyroid dysfunction • Diabetes • Cardiovascular, renal, or liver disease or gallstones • Significant change in body weight < 3 months prior to study entry • Dieting Randomised N = 80 Withdrawals/losses to follow-up • 4/80 (5%); 1/20 in placebo group (non attendance), 3/20 in flutamide group (increase in transaminases) Baseline data (mean (SD)) BMI: placebo group 37 (5), metformin group 35 (4), flutamide group 33 (4), metformin + flutamide group 35 (5) Hirsutism score: placebo group 9.3 (4.8), metformin group 13.0 (8.9), flutamide group 14.6 (6.8), metformin + flutamide group 14.5 (6.5) Total testosterone (nmol/L): placebo group 0.60 (0.27), metformin group 0.65 (0.37), flutamide group 0.72 (0.23), metformin + flutamide group 0.67 (0.17) Androstenedione (nmol/L): placebo group 304 (122), metformin group 314 (148), flutamide group 385 (151), metformin + flutamide group 389 (137) DHEAS (μmol/ml): placebo group 2.0 (0.1), metformin group 2.2 (0.5), flutamide group 2.9 (1.4), metformin + flutamide group 2.8 (1.5) SHBG (nmol/L): placebo group 21.1 (16.8), metformin group 19.9 (11.7), flutamide group 25.4 (8.7), metformin + flutamide group 22.6 (11.6)
Interventions	**Intervention** • Placebo for 12 months (20) **Comparator 1**

	• Metformin 850 mg b.i.d. for 12 months (20) **Comparator 2** • Flutamide 250 mg b.i.d. for 12 months (20) **Comparator 3** • Metformin 850 mg b.i.d. + flutamide 250 mg b.i.d. for 12 months (20) Women were placed, for the first month, on a standardised hypocaloric diet (1200 to 1420 kcal/daily). After this period and while continuing dietary treatment, they were randomly placed in the treatment arms All women were advised in writing to use non hormonal contraception throughout the study
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Plasma glucose 2. Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides 3. Computerised tomography of body fat distribution 4. OGTT 5. Serum testosterone, SHBG, androstenedione, DHEAS * 6. Hirsutism and menses * 7. Anthropometric parameters (height, weight, waist and hip circumferences) * 8. Compliance with diet and pharmacological treatment 9. Questionnaire of physical activity * Denotes outcomes prespecified for this review
Notes	40 women were included earlier in a previous study, Gambineri 2004

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 3971): "PCOS women were randomized to receive...". "The allocation sequence of the treatments was decided by a third party (A.V.) before the recruitment of the patients by random number tables." Comment: probably done
Allocation concealment (selection bias)	High risk	As a third party had access to the random number tables, allocation concealment might not have been adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 3971): "Therefore, the metformin plus flutamide group took four tablets per day, whereas the other groups took two tablets per day. Metformin, flutamide, and placebo were packaged in sim-

		ilar preparations, and patients were blinded to the treatments." Comment: although the packages looked similar, the dosing was not similar, therefor it is unclear if the blinding was effective
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 3971): "All these assessments were performed by the same researcher (A. G.), blinded to the treatment, throughout the study." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/80 (5%); 1/20 in placebo group (non attendance), 3/20 in flutamide group (increase in transaminases). Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 3979): "We are indebted to Laboratori Guidotti SpA, Pisa, Italy, and Ipsen SpA, Milano, Italy, who provided metformin, flutamide, and placebo tablets. " Baseline imbalance in F-G score, lower in placebo group Comment: we judged this as at unclear risk of bias

Ganie 2004

Methods	Randomised, open-label, active-controlled trial Setting Departments of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India Date of study 2000-2001. Duration of intervention 6 months
Participants	N = 82 Mean age = 23 years **Inclusion criteria of the trial** • Women with PCOS according to National Institutes of Health National Institute of Child Health and Human Development 1990 consensus conference criteria (Zawadski 1992) • Presence of menstrual disturbances (oligo-/amenorrhoea) and hirsutism (Ferriman-Gallwey score ≥ 8) **Exclusion criteria of the trial** • Cushing's syndrome • Nonclassical adrenal hyperplasia • Thyroid dysfunction • Hyperprolactinaemia • Androgen-secreting tumours • Any hormonal preparations or drug(s) known or suspected to affect reproductive or metabolic functions within 60 days of study entry • Diabetes mellitus or renal, hepatic, or cardiac dysfunction Randomised N = 82 Withdrawals/losses to follow-up • 13/82 (16%); 6/41 in metformin group, 7/41 in spironolactone group • Dropped out; 4/41 in metformin group, 2/41 in spironolactone group • Incomplete data, lost to follow-up; 2/41 in metformin group, 5/41 in spironolactone group Baseline data (mean (SD)) BMI: metformin group 26.5 (5.6), spironolactone group 25.9 (5.0) F-G score: metformin group 12.5 (4.9), spironolactone group 12.9 (3.2) Testosterone (nmol/L): metformin group 3.25 (1.59), spironolactone group 3.57 (0.34) DHEAS (μmol/L): metformin group 7.0 (3.32), spironolactone group 6.93 (2.75)
Interventions	**Intervention** • Metformin 500 mg b.i.d. for 6 months (41) **Comparator** • Spironolactone 25 mg b.i.d.for 6 months (41) All married/sexually active women were advised to use barrier contraception throughout the study
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Anthropometric assessment (body weight, height, BMI, waist/hip ratio) *

	3. Oral glucose tolerance test 4. Serum T4, TSH, LH, FSH, prolactin, testosterone, DHEAS, cortisol, blood counts, electrolytes, lipids, liver and kidney functions * 5. Adverse events * 6. Ultrasonography for ovary cysts * Denotes outcomes prespecified for this review
Notes	Inconsistency with 'incomplete data/ lost to follow-up' between Fig 1 and text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2757): "After baseline evaluation, eligible patients were randomized in an open-labeled manner by a simple randomization process using computer-generated random number allocation according to CONSORT guidelines." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (page 2757): "The allocation concealment was maintained until OGTT was done." Comment: the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 2757): "open-labeled manner" Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 2758): "The same observer, while being blind to the previous score, did follow-up scoring" and "open-labeled manner" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement

Ganie 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13/82 (16%); 7/41 in spironolactone group, 6/41 in metformin group, reasons reported. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ghosh 2008

Methods	Randomised, active-controlled trial Setting Royal Berkshire NHS Foundation Trust, Reading, Berkshire, UK Date of study Not reported. Duration of the intervention 6 months
Participants	N = 24 Mean age = 33 years **Inclusion criteria of the trial** • Overweight women with PCOS **Exclusion criteria of the trial** • On OCP or antiandrogens Randomised N = 24 Withdrawals/losses to follow-up • Not reported Baseline data (mean) BMI: low carbohydrate diet group 33.4, low glycaemic index diet group 31.5 Basal menstrual cycle lengths: low carbohydrate diet group 12 weeks, low glycaemic index diet group 14 weeks
Interventions	**Intervention** • Low carbohydrate diet for 6 months **Comparator** • Low glycaemic index diet for 6 months
Outcomes	Assessments (7): baseline, month 1, 2, 3, 4, 5, and 6 **Outcomes of the trial** (as reported) 1. Weight, BMI

	* 2. Biochemical and endocrine parameters (insulin, testosterone, lipids) * 3. Food diaries 4. Menstrual cycle * *Denotes outcomes prespecified for this review
Notes	Abstract to conference proceedings, limited data reported, unclear how many women were hirsute. See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 279): "A randomised trial comparing..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

Grant 2010

Methods	Randomised, active-controlled trial Setting Department of Diabetes and Endocrinology, Eastbourne District General Hospital, Kings Drive, Eastbourne, East Sussex, UK Date of study Not reported. Duration of intervention 30 days
Participants	N = 42 Mean age = 26 years **Inclusion criteria of the trial** • Women with PCOS, diagnosed based on Rotterdam Criteria PCOS 2004 **Exclusion criteria of the trial** • Not reported Randomised N = 42 Withdrawals/losses to follow-up • 1/42 (2%); 0/21 in spearmint tea group, 1/21 in camomile tea group because of dislike of the flavour Baseline data (mean (SD)) F-G score: spearmint tea group 17, camomile tea group 17 DLQI index: spearmint tea group 17, camomile tea group 18 Free testosterone (pg/ml): spearmint tea group 5.12 (2.14), camomile tea group 4.98 (2.84) Testosterone (ng/ml): spearmint tea group 0.81 (0.39), camomile tea group 0.87 (0.40) DHEAS (µmol/L): spearmint tea group 184.5 (82.1), camomile tea group 179.5 (85.3)
Interventions	Assessments (3): baseline, day 15 and 30 **Intervention** • Spearmint tea b.i.d. for 30 days (21) **Comparator** • Camomile tea b.i.d. for 30 days (21)
Outcomes	**Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Dermatology Quality of Life Index * 3. Androgen hormone levels * 4. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Grant 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote (page 187): "... were randomized by computer equally into to two groups..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 187): "...with a standardized content of dried tea leaves"... "The researchers were blinded as to the type of tea" Comment: the report did not provide detail on blinding of participants nor the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 187): "The researchers were blinded as to the type of tea". Participants were not blinded. Outcomes were assessed by investigators and participants Comment: uncertainty about the effectiveness of blinding of investigators during the study and the lack of blinding of participants We judged this as at a high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/42 lost to follow-up, reason reported. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Hamzavi 2007

Methods	Randomised, double-blind, within-participant, active-controlled trial Setting Department of Dermatology and Skin Science, University of British Columbia and the Vancouver Coastal Health Research Institute, Canada Date of study Not reported. Duration of intervention 6 months
Participants	N = 33 Mean age = 41 years **Inclusion criteria of the trial** • Women > 18 years with unwanted facial hair who carried out hair removal of any kind to their upper lip at least twice a week • Predominantly dark facial hair **Exclusion criteria of the trial** • Presence of tattoos over or near the upper lip • Photosensitivity • Severe acne vulgaris • Immunosuppression • Pregnancy • Lactation Randomised N = 33 Withdrawals/losses to follow-up • 2/33 (6%); 1 because of hyperpigmentation and 1 lost to follow-up Baseline data Nothing reported other than skin type and age
Interventions	**Intervention** • Long-pulsed alexandrite laser every 4 weeks + eflornithine 13.9% cream b.i.d. for 6 months **Comparator** • Long-pulsed alexandrite laser every 4 weeks + vehicle cream b.i.d. for 6 months Participants were required to discontinue all other modalities of hair removal for 2 weeks before the first laser treatment session and then throughout the 26-week study period
Outcomes	Assessments (7): baseline, week 4, 8, 12, 16, 20, and 24 **Outcomes of the trial** (as reported) 1. Investigator global assessment; 4-point Likert scale * 2. Subjective assessments; 4-point Likert scale * 3. Hair counts * 4. Adverse events * * Denotes outcomes prespecified for this review
Notes	Although this study does include laser, it includes laser in both treatment arms and investigates eflornithine cream as add-on therapy

Hamzavi 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 55): "... assignment of the color-coded tubes to either the right or left side of the upper lip was done randomly by coin toss" Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "Coin toss. One toss for each patient to be recruited. 2. Record the successive results of each coin toss. 3. Put the result of the coin toss in successive numbered sealed envelopes. The coin toss result determined which side of the face was randomized to receive the treatment cream in a blinded manner. 4. As each patient was enrolled, each successive envelope was opened." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 55): "All tubes of the same color code contained the same product, namely either eflornithine HCl 13.9% cream or vehicle cream; the only label on the tubes was the official study title. Patients and investigators were blinded as to the overall color code scheme, and the sealed code was broken only after all statistical analyses." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Hamzavi 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 55): "Patients and investigators were blinded as to the overall color code scheme, and the sealed code was broken only after all statistical analyses." Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/33 (6%), reasons reported. Per-protocol analysis (within participant comparison) Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 54): "Dr Lui has been a speaker for Barrier Therapeutics Canada. Dr Hamzavi has been a speaker for Shire Pharmaceuticals and SkinMedica. Dr Shapiro is a speaker for Shire Pharmaceuticals and Barrier Therapeutics Canada and has served as a consultant for SkinMedica. " Comment: Shire Pharmaceuticals is the manufacturer of eflornithine 13.9% cream and a potential risk of bias cannot be excluded

Harborne 2003

Methods	Randomised, active-controlled trial Setting University Department of Obstetrics and Gynecology, Royal Infirmary, Glasgow, Scotland, UK Date of study Not reported. Duration of intervention 12 months
Participants	N = 52 Mean age = 31 years **Inclusion criteria of the trial** • Women with PCOS, whose primary complaint was hirsutism

	• The diagnosis of PCOS included at least 2 of the 3 following features: oligomenorrhoea/amenorrhoea, polycystic ovaries on ultrasound (2), or an elevated free androgen index **Exclusion criteria of the trial** • Contraindications to either metformin or Dianette (including BMI > 38) • Use of oral contraception or metformin within the previous 3 months • Thyroid dysfunction • Hyperprolactinaemia • Diabetes mellitus, or late onset congenital adrenal hyperplasia • Medication known to affect gonadal or adrenal function, or carbohydrate or lipid metabolism Randomised N = 52 Withdrawals/losses to follow-up • 18/52 (35%); 10/26 in CPA + EE group, 8/26 in metformin group • Weight gain; 5/26 in CPA + EE group, 0/26 in metformin group • Blood pressure increase; 1/26 in CPA + EE group, 0/26 in metformin group • Depression; 1/26 in CPA + EE group, 0/26 in metformin group • Chest pain; 1/26 in CPA + EE group, 0/26 in metformin group • Pregnancy; 0/26 in CPA + EE group, 3/26 in metformin group • Gastrointestinal side effects; 0/26 in CPA + EE group, 8/26 in metformin group • Lost to follow-up; 2/26 in CPA + EE group, 3/26 in metformin group Baseline data (mean) F-G score: CPA + EE group 22.8, metformin group 20.3 BMI: CPA + EE group 31.8, metformin group 31.7 Testosterone (ng/ml): CPA + EE group 3.52, metformin group 3.19 SHBG (nmol/L): CPA + EE group 31.4, metformin group 30.4 Androstenedione (ng/ml): CPA + EE group 11.6, metformin group 11.6 DHEAS (μmol/L): CPA + EE group 7.2, metformin group 6.8
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 12 months (26) **Comparator** • Metformin 500 mg 3 times a day for 12 months (26) Women were also advised to use barrier contraception if randomised to metformin
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Anthropometric measurements of height, weight (BMI), waist/hip ratio, blood pressure * 2. Ferriman-Gallwey score and hair diameter * 3. Sebum excretion rate 4. Adverse effects * 5. Participants' perception/status (hirsutism; acne; effects of treatment); VAS * 6. Serum concentrations of insulin, glucose, testosterone, SHBG, androstenedione,

	DHEAS, 17-hydroxyprogesterone, cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor-binding protein 3 (IGFBP-3) * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 4117): "Patients were block-randomized (n=10/block) in a 1:1 ratio... Randomization was by random number tables" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 4117): "...patient number treatment codes were held by a third party and were allocated individually after obtaining written consent. A list of codes was kept by a third party, and patient names were checked after completion of the trial" Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	18/52 (35%); 10/26 in CPA + EE group, 8/26 in metformin group. Per-protocol analysis Comment: although balanced, high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section

		appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Heiner 1995

Methods	Randomised, double-blind, active-controlled trial Setting Departments of Obstetrics and Gynecology, Internal Medicine, and Anatomy, University of California School of Medicine, Los Angeles, California, US Date of study Not reported. Duration of intervention 24 weeks
Participants	N = 141 screened, 74 randomised Mean age = 30 years **Inclusion criteria of the trial** • 18 to 45 years • Any racial background • Hirsutism in excess of immediate female blood relatives • Moderate or greater hirsutism (defined by hormonal FG score $\geq$ 10) • Negative serum pregnancy test • Willingness to use a barrier method of contraception if appropriate • Willingness to refrain from hair removal procedures for at least 3 days before each study visit **Exclusion criteria of the trial** • Use of sex steroids, adrenal steroids, or spironolactone < 3 months before the study • Past or current malignancy, cerebral vascular accident, or coronary artery disease • Uncontrolled hypertension (blood pressure, > 140/95 mmHg) • Treated or untreated thyroid disease, diabetes mellitus, or drug/alcohol abuse • Active liver disease (aspartate aminotransferase or alanine aminotransferase, > 50 U/L) or gallbladder disease (prior cholecystectomy permitted) • Cigarette use, if subject older than 35 years during the study • Ovarian failure (FSH, > 50 IU/L) • Acquired adrenal hyperplasia (17-hydroxyprogesterone > 25 nmol/L 1 h after 250 μg iv bolus of Cortrosyn • Hypercortisolism (fasting cortisol >140 nmol/L 1 mg dexamethasone administered at 2300 h the evening before testing) • Cervical dysplasia (moderate or worse) • Current participation in another clinical trial Randomised N = 74 Withdrawals/losses to follow-up • 10/74 (14%); unclear from which groups • After 8 weeks further 8/64 (13%), unclear from which group Baseline data (mean (SE))

	F-G score: nafarelin spray + OCP group 21.9 (1.6), placebo spray + OCP 23.3 (1.7), nafarelin spray + placebo pill group 24.3 (2.0), placebo spray + placebo pill group 24.9 (1.5)
Interventions	**Intervention** • Nafarelin nasal spray 400 μg b.i.d. + OCP (norethindrone 1 mg + ethinyl estradiol) for 24 weeks (16) **Comparator 1** • Placebo nasal spray b.i.d. + OCP (norethindrone 1 mg + ethinyl estradiol) for 24 weeks (16) **Comparator 2** • Nafarelin nasal spray 400 μg b.i.d. + placebo OCP for 24 weeks (14) **Comparator 3** • Placebo nasal spray b.i.d. + placebo OCP for 24 weeks (18)
Outcomes	Assessments (4): baseline, week 8, 16, and 24 **Outcomes of the trial** (as reported) 1. Serum testosterone, free testosterone, androstenedione, DHEAS, LH, FSH, estradiol, SHBG * 2. Ferriman-Gallwey score * 3. Hair diameter; measured by light microscopy * 4. Hot flush monitoring 5. Bone mineral density of the lumbar spine * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 3413): "...assigned by computer-generated randomization code..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 3412-13): "...double-masked. .." "... the placebo spray contained only the vehicle materials...placebo tablets were

		identical in appearance" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 3412-13): "...double-masked. .." "... the placebo spray contained only the vehicle materials...placebo tablets were identical in appearance" Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote (page 3413): "Intention-to-treat analysis was employed. The results from women who were randomized but dropped out of the study before 8 weeks were not analyzed" 10/74 (14%) dropped out < 8 weeks. Losses 8/64 after this period but included in analysis Comment: early losses not included in analysis; high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 3412): "This work was supported by Syntex Laboratories and USPHS Grant RR-865. Two investigators were employed by Syntex Laboratories, Inc Comment: a potential risk of bias cannot be excluded

Hoeger 2004

Methods	Randomised, placebo-controlled trial Setting University of Rochester School of Medicine and Dentistry and School of Nursing, Rochester, New York, US Date of study Not reported. Duration of intervention 48 weeks
Participants	N = 273 screened, 38 randomised Mean age = 28 years **Inclusion criteria of the trial** • Overweight or obese women with PCOS • Polycystic ovary syndrome was diagnosed by fewer than 6 menses per year and evidence of hyperandrogenism • Minimum body mass index (BMI) of 25 kg/m^2 **Exclusion criteria of the trial** • Any hormonal medication within the last 2 months before entry into the study • Subjects actively dieting at time of entry Randomised N = 38 Withdrawals/losses to follow-up • 15/38 (39%); 4/9 in metformin group, 5/11 in lifestyle + placebo group, 4/9 in lifestyle + metformin group, 2/9 placebo group • Reasons; adverse events, time commitment, pregnancy, or were unable to be contacted Baseline data (mean (SD)) BMI: metformin group 37.1 (4.9), lifestyle + placebo group 40 (7.4), lifestyle + metformin group 41.7 (6.2), placebo group 37.1 (4.6) Waist/hip ratio: metformin group 0.96 (0.07), lifestyle + placebo group 0.9 (0.06), lifestyle + metformin group 0.89 (0.07), placebo group 0.94 (0.09) Testosterone (ng/dl): metformin group 61.2 (23.8), lifestyle + placebo group 56.9 (18.9), lifestyle + metformin group 70.0 (17.1), placebo group 58.1 (17.3) SHBG (nmol/L): metformin group 22.42 (7.15), lifestyle + placebo group 32.84 (14.96), lifestyle + metformin group 29.91 (11.74), placebo group 31.19 (10.13)
Interventions	**Intervention** • Metformin 850 mg b.i.d. for 48 weeks (9) **Comparator 1** • Lifestyle modification + placebo b.i.d. for 48 weeks (11) **Comparator 2** • Lifestyle modification + metformin 850 mg b.i.d. for 48 weeks (9) **Comparator 3** • Placebo b.i.d. for 48 weeks (9)
Outcomes	Assessments (8): baseline and every 4 weeks until 48 weeks **Outcomes of the trial** (as reported) 1. Evaluate compliance with medication 2. Body weight 3. Side effects *

	4. Menstrual diaries * 5. Glucose, insulin, testosterone, SHBG, FAI, pregnanediol glucuronide * 6. Ferriman-Gallwey score * *Denotes outcomes prespecified for this review
Notes	All groups had a mean modified Ferriman-Gallwey score > 10, data to be estimated from Fig 2 in the paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 423): " The randomization schedule was computer generated in blocks by an independent pharmacy representative, and block schedule was blinded to the investigators" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 423): "... independent pharmacy representative... packaged and labeled according to subject number by the pharmacy" Comment: form of central allocation, probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 423): "Metformin hydrochloride ... formulated with the appropriate dose into capsules by Investigation Pharmacy Service at the University of Rochester. Identically appearing placebo capsules were also formulated" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention (i.e. metformin or placebo) a participant received, however, lifestyle modification was not blinded for participants and investigators We judged this as at unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 423): "Metformin hydrochloride ... formulated with the appropriate dose into capsules by Investigation Pharmacy Service at the University of Rochester. Identically appearing placebo capsules were

		also formulated“ ... ”Drug and placebo were packaged and labeled according to subject number by the pharmacy in a double-blind fashion.“ Although participants and investigators were blinded for metformin or placebo, they were not blinded for lifestyle modification and OCP Comment: we judged this as at unclear risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	15/38 (39%); 4/9 in metformin group, 5/11 in lifestyle + placebo group, 4/9 in lifestyle + metformin group, 2/9 placebo group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Unclear risk	Although participants returned monthly to evaluate compliance and side effects, the side effects were inadequately reported Comment: we judged this as at unclear risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Hoeger 2008

Methods	2 randomised, placebo-controlled trials Setting Departments of Obstetrics and Gynecology University of Rochester Medical Center, Rochester, New York, US Date of study Enrolment study 1: August 2002 until September 2003, for study 2: May 2006 until July 2007. Duration of intervention in both studies 24 weeks
Participants	N = 79 (study 1: 43, study 2: 36) Mean age = 16 years in study 1 and 15 years in study 2 **Inclusion criteria of the trial** • Obese adolescent women with PCOS (12 to 18 years) • BMI above the 95th percentile • Evidence of menstrual irregularity (fewer than 8 menses in the preceding year) • Clinical or biochemical evidence of hyperandrogenism **Exclusion criteria of the trial** • Other causes of hyperandrogenism and menstrual irregularity • Hormonal therapy or insulin sensitisers < 2 months prior to study entry Randomised

	N = 79 Withdrawals/losses to follow-up Study 1 • 9/43 (21%); 4/10 in metformin group, 1/11 in placebo group, 1/11 in OCP group, 3/11 in lifestyle group • Lost to follow-up; 2/10 in metformin group, 1/11 in placebo group, 1/11 in OCP group, 0/11 in lifestyle group • Time commitment; 0/10 in metformin group, 0/11 in placebo group, 0/11 in OCP group, 3/11 in lifestyle group • Personal reasons; 2/10 in metformin group, 0/11 in placebo group, 0/11 in OCP group, 0/11 in lifestyle group Study 2 • 4/36 (11%); 2/18 in metformin group, 2/18 in placebo group • Gastrointestinal complaints; 1/18 in metformin group, 1/18 in placebo group • Dose reduction; 1/18 in metformin group, 1/18 in placebo group Baseline data study 1 (mean (SD)) BMI: metformin group 34.3 (6.5), placebo group 36.1 (7.5), OCP group 37.8 (5.1), lifestyle group 37.8 (8.2) F-G score: metformin group 7.8 (2.6), placebo group 12.5 (5.3), OCP group 9.8 (3.5), lifestyle group 9.2 (1.9) Testosterone (ng/dl): metformin group 51.3 (13.0), placebo group 61.2 (30.5), OCP group 63.0 (23.0), lifestyle group 63.9 (29.6) SHBG (nmol/L): metformin group 23.5 (19.1), placebo group 17.7 (7.4), OCP group 18.0 (11.7), lifestyle group 14.6 (12.6) Baseline data study 2 (mean (SD)) BMI: metformin group 35.7 (4.9), placebo group 34.1 (4.3) F-G score: metformin group 10.3 (4.3), placebo group 7.9 (3.1) Testosterone (ng/dl): metformin group 83.2 (27.8), placebo group 102.6 (22.1) SHBG (nmol/ml): metformin group 9.6 (11.9), placebo group 10.1 (10.9)
Interventions	**Study 1** **Intervention** • Metformin 850 mg b.i.d. for 24 weeks (10) **Comparator 1** • Placebo b.i.d. for 24 weeks (11) **Comparator 2** • OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) for 24 weeks (11) **Comparator 3** • Lifestyle modification for 24 weeks (11) **Study 2** **Intervention** • Metformin 1000 mg b.i.d. for 24 weeks (18) **Comparator 1** • Placebo b.i.d. for 24 weeks (18) All subjects in study 2 were assigned to lifestyle intervention and placed on an OCP containing 30 μg of ethinyl estradiol and 3.0 mg drospirenone
Outcomes	**Study 1** Assessments (2): baseline and week 24

	Outcomes of the trial (as reported) 1. Total testosterone, SHBG, lipids, cholesterol, LDL cholesterol, HDL cholesterol, triglycerides * 2. Plasminogen activator inhibitor 1 and highly sensitive C-reactive protein 3. Glucose and oral glucose intolerance test 4. Percentage body fat (dual-energy x-ray absorptiometry) 5. Computed tomogram (CT) for intra-abdominal fat 6. Menstrual data * **Study 2** Assessments (2): baseline and week 24 **Outcomes of the trial** (as reported) 1. Total testosterone, SHBG, lipids, cholesterol, LDL cholesterol, HDL cholesterol, triglycerides * 2. Plasminogen activator inhibitor 1 and highly sensitive C-reactive protein 3. Glucose and oral glucose intolerance test 4. Percentage body fat (dual-energy x-ray absorptiometry) 5. Transabdominal ultrasound to assess ovarian volume 6. Menstrual data * *Denotes outcomes prespecified for this review
Notes	No subject in the single treatment trial was also included in the combination treatment trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study 1 quote (page 4300): "...were randomized to one of four arms by random number assignment..." Comment: probably done Study 2 quote (page 4301): "Subjects were assigned by a random number table to metformin or placebo" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Study 1 quote (page 4300): "Assignment to metformin or placebo was blinded to subject and investigator". No information on assignment to OCP or lifestyle programme Study 2. No extra information The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment

		for both studies, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study 1 quote (page 4300): "Metformin and placebo capsules were prepared by the Investigational Drug Pharmacy service at the University of Rochester using a commercially available powdered form of metformin or a lactose powder for the placebo, dispensed into identical capsules" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention regarding metformin or placebo a participant received, however, lifestyle modification and OCP were not blinded for participants and investigators. We judged this as at unclear risk of bias Study 2 quote (page 4301): "Assignment. .. blinded to subject and investigator. ... capsules prepared by Investigational Drug Pharmacy service at the University of Rochester ... powdered ... lactose powder for placebo, dispensed into identical capsules" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. We judged this as at a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study 1 quote (page 4300): "Metformin and placebo capsules were prepared by the Investigational Drug Pharmacy service at the University of Rochester using a commercially available powdered form of metformin or a lactose powder for the placebo, dispensed into identical capsules" Although participants and investigators were blinded for metformin or placebo, they were not blinded for lifestyle modification and OCP Comment: we judged this as at an unclear risk of bias Study 2 quote (page 4301): "Assignment. .. blinded to subject and investigator. ...

Hoeger 2008 (*Continued*)

		capsules prepared by Investigational Drug Pharmacy service at the University of Rochester ... powdered ... lactose powder for placebo, dispensed into identical capsules" Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses/withdrawals 13/79 (16%) Study 1: 9/43 (21%); 4/10 in metformin group, 1/11 in placebo group, 1/11 in OCP group, 3/11 in lifestyle group. Per-protocol analysis Study 2: 4/36 (11%); 2/18 in metformin group, 2/18 in placebo group. Per-protocol analysis Comment: significant drop-out rate combined with per protocol analysis poses an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 4305): "K.H. reports receiving lecture fees from EMD Serono and Organon Pharmaceuticals". Organon is a manufacturer of the OCP used in study 1 Comment: a potential risk of bias cannot be excluded

Holdaway 1985

Methods	Randomised, double-blind, active-controlled, cross-over trial Setting Department of Endocrinology, Auckland Hospital, Auckland, New Zealand Date of study Not reported. Duration of randomised part (second part) 12 months (cross-over at 6 months)
Participants	N = 35 Mean age = not reported **Inclusion criteria of the trial**

	• Moderate to severe hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 35 Withdrawals/losses to follow-up • 6/35 (17%); 1/35 during the first 9 months (the non-randomised part), 5/35 in the randomised part (next 12 months) • Migraine; 1/35 • Poor response to treatment; 3/35 • Depression; 1/35 • No reason; 1/35 Baseline data Nothing reported
Interventions	All participants received for first 9 months an OCP (50 µg ethinyl estradiol and 2 mg cyproterone acetate) + 100 mg cyproterone acetate on days 5 to 14 of the menstrual cycle. After the 9 months participants were randomised in a cross-over study (2 treatment periods of 6 months) **Intervention** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) + 25 mg CPA **Comparator** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) + placebo
Outcomes	Assessments (8): baseline, month 3, 6, 9, 12, 15, and 18 **Outcomes of the trial** (as reported) 1. Serum testosterone, SHBG, androstenedione, DHEAS * 2. Haematology profile, serum electrolytes, liver function tests 3. Ferriman-Gallwey score * 4. Subjective self rating; 4-point Likert scale * 5. Hair growth assessed by photographic method * 6. Weight, blood pressure 7. Adverse events * 8. Relapse * Denotes outcomes prespecified for this review
Notes	No wash-out period after first 9 months, thereafter cross-over design, but with no wash-out period. No separate data reported for baseline and end of treatment period for each of the 3 time periods. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement

Holdaway 1985 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 523): "... were randomised..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 523): "...double-blind crossover study..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1016): "...double-blind crossover study..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/35 (17%); 1/35 during the first 9 months (non-randomised period), 5/35 in the randomised period (subsequent 12 months), reasons reported. Per-protocol analysis Comment: significant drop-out rate combined with per protocol analysis poses an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Other bias	Low risk	Quote (page 528): "Cyproterone acetate and Diane® were provided by Schering (New Zealand) Ltd., who also provided reagents for cyproterone acetate assay" Comment: we judged this as at a low risk of bias

Huber 1985

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology and Department of Dermatology, University of Vienna, Vienna, Austria Date of study Not reported. Duration of intervention 6 months
Participants	N = 10 Mean age = not reported **Inclusion criteria of the trial** • Hirsute women **Exclusion criteria of the trial** • Not reported Randomised N = 10 Withdrawals/losses to follow-up • Not reported Baseline data Nothing reported
Interventions	**Intervention** • Cyproterone acetate 300 mg im + OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) for 6 cycles **Comparator** • Cyproterone acetate 100 mg orally for 10 days + OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) for 6 cycles
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Serum testosterone, DHEAS, prolactin * 2. Hirsutism assessment by determination of hair diameter * *Denotes outcomes prespecified for this review
Notes	Abstract. Limited data are provided. Unclear if there were 2 groups of 5, see Table 3

Risk of bias

Huber 1985 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 200): " treated at random..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

Ibáñez 2002

Methods	Randomised, open-label, active-controlled trial Setting Endocrinology Unit and Hormonal Laboratory, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain Date of study Not reported. Duration of intervention 9 months
Participants	N = 31 Mean age = 19 years **Inclusion criteria of the trial**

	• Hyperinsulinaemia on standard 2-hour oral glucose tolerance testing, defined as peak serum insulin concentration greater than 150 U/ml and/or mean serum insulin greater than 84 mU/L • Normal oral glucose tolerance • Ovarian hyperandrogenism as defined by hirsutism (score ≥ 8 on Ferriman-Gallwey scale) + elevated serum androstenedione, total testosterone, and/or free androgen index, 17-hydroxyprogesterone (17-OHP) hyper-response (>160 ng/dl) to leuprolide acetate, a GnRH agonist **Exclusion criteria of the trial** • BMI > 25 kg/m^2 • Thyroid dysfunction • Hyperprolactinaemia • A family or personal history of diabetes mellitus • Late-onset congenital adrenal hyperplasia • Medication known to affect gonadal or adrenal function, or carbohydrate or lipid metabolism. Randomised N = 31 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: flutamide group 22.3 (0.6), metformin group 22.5 (0.8), flutamide + metformin group 21.2 (0.6) F-G score: flutamide group 14.1 (1.0), metformin group 18.0 (1.6), flutamide + metformin group 16.2 (0.9) Testosterone (ng/dl): flutamide group 108 (12), metformin group 132 (17), flutamide + metformin group 104 (6) SHBG (μg/dl): flutamide group 0.8 (0.1), metformin group 0.7 (0.1), flutamide + metformin group 0.9 (0.1) Androstenedione (ng/dl): flutamide group 272 (19), metformin group 274 (26), flutamide + metformin group 336 (27) DHEAS (μg/dl): flutamide group 231 (15), metformin group 264 (31), flutamide + metformin group 301 (20)
Interventions	**Intervention** • Flutamide 250 mg once daily for 9 months (10) **Comparator 1** • Metformin 1275 mg once a day for 9 months (8) **Comparator 2** • Flutamide 250 mg + metformin 1275 mg once a day for 9 months (13)
Outcomes	Assessments (5): baseline, month 1, 3, 6, and 9 **Outcomes of the trial** (as reported) 1. Serum LH, FSH, estradiol, testosterone, androstenedione, DHEAS, SHBG, and lipid profile * 2. Insulin sensitivity (calculated from fasting glucose and insulin data using the homeostasis model assessment (HOMA) 3. Blood count and liver and kidney function

	4. Ovulation assessment * 5. Ferriman-Gallwey score * 6. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2981): "...were randomized to receive..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 2871): "...open-labeled..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 2871): "...open-labeled..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk

Ibáñez 2002 (*Continued*)

		of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ibáñez 2003

Methods	Randomised, open-label, active-controlled trial Setting Endocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain Date of study Not reported. Duration of intervention 9 months
Participants	N = 30 Mean age = 16 years **Inclusion criteria of the trial** • Hyperinsulinaemia on a standard 2-hour oral glucose tolerance testing, defined as peak serum insulin levels > 150 U/ml (29) and/or mean serum insulin > 84 mU/L • Ovarian hyperandrogenism as defined by a- or oligo-menorrhoea (duration of menstrual cycles 45 d) and/or hirsutism (Ferriman and Gallwey score > 8, elevated serum androstenedione, total testosterone, and/or free androgen index and 17-hydroxyprogesterone hyper response (> 160 ng/dl) to GnRH agonist (leuprolide acetate) **Exclusion criteria of the trial** • BMI > 25 kg/m^2 • Thyroid dysfunction • Cushing's syndrome • Hyperprolactinaemia • Glucose intolerance • Family or personal history of diabetes mellitus • Late onset congenital adrenal hyperplasia • Intake of medication known to affect gonadal or adrenal function, or carbohydrate or lipid metabolism; abnormal blood count or serum electrolytes • Abnormal results in screening tests for liver and kidney function Randomised N = 30 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: group 1 21.7 (0.4), group 2 21.7 (0.5) F-G score: group 1 15.5 (1.0), group 2 14.4 (1.0) SHBG (µg/dl): group 1 1.0 (0.1), group 2 0.9 (0.1) Testosterone (ng/dl): group 1 126 (12), group 2 136 (9) Androstenedione (ng/dl): group 1 271 (24), group 2 296 (33) DHEAS (µg/dl): group 1 247 (18), group 2 255 (23)

Interventions	**Intervention group 1** • 3 months no treatment and then 9 months flutamide 125 mg a day + metformin 1275 mg per day (14) **Comparator** • 9 months flutamide 125 mg a day + metformin 1275 mg per day + 3 months no treatment (16)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Fasting glucose, insulin, LH, FSH, SHBG, DHEAS, estradiol, testosterone, androstenedione, and lipid profile * 2. Insulin sensitivity (calculated from fasting glucose and insulin data using the homeostasis model assessment (HOMA) 3. Blood count and liver and kidney function 4. Ovulation assessment * 5. Waist/hip ratio 6. Body composition (dual-energy x-ray absorptiometry) 7. Ferriman-Gallwey score * 8. Adverse events * * Denotes outcomes prespecified for this review
Notes	Intervention and comparator are identical, participants "randomised to" timing of start of treatment. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2601): "...randomized to..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement

Ibáñez 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 2601): "...open-labeled..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 2601): "...open-labeled..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ibáñez 2009

Methods	Randomised, double-blind, placebo-controlled trial Setting Endocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain Date of study Not reported. Duration of intervention 24 months
Participants	N = 38 Mean age = 20 years **Inclusion criteria of the trial** • Hyperinsulinaemia on a standard 2-hour oral glucose tolerance test, defined as peak serum insulin levels > 150 U/ml and/or mean serum insulin > 84 U/ml • Ovarian androgen excess, as defined by: 1) hirsutism (Ferriman-Gallwey score > 8, amenorrhoea (menses absent for more than 3 months), or oligomenorrhoea (menstrual cycles > 45 d), 2) high serum androstenedione, total testosterone, or free androgen index and 3) a 17-hydroxyprogesterone hyper response (> 160 ng/dl) to a GnRH agonist (leuprolide acetate 500 g sc) **Exclusion criteria of the trial** • Contraceptive or another medication known to affect gonadal or adrenal function, or carbohydrate or lipid metabolism, < 9 months prior to study entry • Evidence of thyroid dysfunction, Cushing's syndrome, or hyperprolactinaemia • Glucose intolerance, personal history of diabetes mellitus

	• Late-onset adrenal hyperplasia • Anaemia • Abnormal serum electrolytes • Abnormal screening results for liver or kidney function • Abnormal echocardiogram Randomised N = 38 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: pioglitazone group 17.7 (1), placebo group 16.4 (0.9) F-G score: pioglitazone group 24.3 (0.6), placebo group 23.1 (0.6) Testosterone (nmol/L): pioglitazone group 2.9 (0.2), placebo group 2.8 (0.2) SHBG (nmol/L): pioglitazone group 35 (3), placebo group 37 (3) Androstenedione (nmol/L): pioglitazone group 16.4 (1.3), placebo group 15.9 (1.1) DHEAS (μmol/L): pioglitazone group 7.1 (0.8), placebo group 7.2 (0.6)
Interventions	**Intervention** • Pioglitazone 7.5 mg once a day + transdermal contraceptive (ethinyl estradiol 600 μg + norelgestromin 6 mg) + metformin 850 mg per day + flutamide 62.5 mg per day for 24 months (19) **Comparator** • Placebo once a day + transdermal contraceptive (ethinyl estradiol 600 μg + norelgestromin 6 mg) + metformin 850 mg per day + flutamide 62.5 mg per day for 24 months (19) After 12 months the transdermal contraceptive was replaced by an oral contraceptive (ethinyl estradiol 30 μg + drospirenone 3 mg)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Height, weight, BMI, waist/hip ratio * 2. Fasting blood glucose, neutrophil and lymphocyte count, serum insulin, LDL- and HDL-cholesterol 3. SHBG, testosterone, androstenedione, 17 hydroxyprogesterone, DHEAS, C-reactive protein, and insulin-like growth factor 1 (IGF-1) were measured together with alanine- and aspartate aminotransferase, γ-glutamyl transpeptidase, and a screening of renal function * 4. Carotid intima-media thickness 5. RBP4 and vaspin 6. Body composition (dual-energy x-ray absorptiometry) and abdominal fat distribution (MRI) 7. Adverse effects * *Denotes outcomes prespecified for this review

Notes	Quote (page 352): "After 18 months, the placebo and pioglitazone subgroups were inversed (pioglitazone cross-over), and the women in those two subgroups were subrandomized (1 : 1 ratio) for replacement of flutamide by a second placebo until month 24. " We only included the first 18 months as there was no wash-out period between the first 18 months and the last 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 352): "...randomized (1 : 1 ratio, as described)..." This refers to reference Ibáñez 2007, which published the 6-month data Quote (page 1711): "...randomly assigned ...After stratification for BMI... randomly assigned [1:1 ratio, Gran Mos program, Barcelona Medical Research Institute" Comment: probably done
Allocation concealment (selection bias)	Low risk	No additional information is provided in this paper, but in the earlier published paper Ibáñez 2007: Quote (page 1711): "The randomization sequence was known only to a pharmacist independent to the study and was thus unknown to the clinically involved investigators" Comment: pharmacy-controlled allocation, probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 352): "All patients and investigators, except for the study statistician (ALB), remained blinded to pioglitazone and flutamide allocation, at least until completion of the present report. Pioglitazone and its placebo were packaged in similar tablets and renewed 3-monthly between 0 and 24 months" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 352): "Pioglitazone and its placebo were packaged in similar tablets" Blinding of participants and key study per-

		sonnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ibáñez 2011B

Methods	Randomised, open-label, active-controlled trial Setting Endocrinology Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain Date of study Not reported. Duration of intervention 4 years, study duration 7 years
Participants	N = 38 Mean age = 8 years **Inclusion criteria of the trial** • Girls with low birth weight and precocious pubarche (PP) • PP due to exaggerated adrenarche, as judged by high serum DHEAS and/or androstenedione levels • Weight below 2.9 kg at term birth (38 to 41 weeks) or below 1 SD for gestational age at preterm birth (33 to 37 weeks) • BMI less than 22 kg/m^2, which corresponds to the 2 SD cutoff in girls aged approximately 8 years • Prepuberty (Tanner stage B1) **Exclusion criteria of the trial** • Family or personal history of diabetes • Evidence for thyroid dysfunction, glucose intolerance, or adrenal hyperplasia • Medication known to affect gonadal function or carbohydrate metabolism Randomised N = 38 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data for whole study group (mean (SEM))

	BMI: 18.4 (0.3) DHEAS (µg/dl): 102 (6)
Interventions	**Intervention** • Metformin for 4 years (425 mg/d at dinner time for 2 years and then 850 mg/d for 2 years), then untreated in years 5 to 7 (19) **Comparator** • Untreated for 5 years, then 1-year treatment with metformin 850 mg/d and no treatment in 7th year (19)
Outcomes	Assessments (15): baseline, every 6 months until end of study **Outcomes of the trial** (as reported) 1. Clinical examination, including height measurement with a Harpenden stadiometer * 2. Fasting insulin, insulin-like growth factor 1 (IGF-1), SHBG, DHEAS, androstenedione, testosterone, lipid profile, and white blood cell count * 3. Body composition; dual-energy x-ray absorptiometry 4. Subcutaneous and abdominal fat distribution (MRI) 5. Presence of polycystic ovarian morphology; abdominal ultrasound 6. Presence of PCOS; presence of clinical/biochemical androgen excess and either oligomenorrhoea (cycles 45 d) or amenorrhoea (no menses for 3 months), besides exclusion of disorders known to potentially cause the same phenotype, such as hyperprolactinaemia and 21-hydroxylase deficiency *Denotes outcomes prespecified for this review
Notes	Intervention and comparator are identical, participants "randomised to" timing of start of treatment. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page E1263): "... randomly assigned...". Authors refer to an earlier paper of 2004 "were assembled by randomization (1:1 ratio). An assignment list was produced before the start of each study by the GranMos program from Barcelona's Medical Research Institute; the investigators followed the sequence in this list, and patients were consecutively included as either untreated or treated according to their positions on this list. At the time of deciding about a patient's inclusion, the investigators had no access to the next treatment assignment in the sequence Comment: probably done

Ibáñez 2011B (*Continued*)

Allocation concealment (selection bias)	Low risk	See above. Form of central allocation, probably done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page E1262): "...open-label..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page E1262-3): "...open-label...". MRI scans were performed by the same operator (blinded to the treatment allocation) , and all images were analyzed by the same radiologist (also blinded to the allocation." Comment: although for certain outcomes, the measurement was blinded for the remaining outcomes the measurement is likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ibáñez 2012

Methods	Randomised, open-label, active-controlled trial Setting Adolescent Endocrinology Unit of Sant Joan University Hospital, Barcelona, Spain Date of study Not reported. Duration of intervention 6 months
Participants	N = 34 Mean age = 16 years **Inclusion criteria of the trial** • Girls with hyperinsulinaemic androgen excess • Hyperinsulinaemia, defined as fasting insulinaemia above 15 µU/ml and/or a peak insulinaemia above 150 µU/ml, and/or mean insulinaemia above 84 µU/ml on a 2-horal glucose tolerance test

	• Presence of both clinical and biochemical androgen excess, as defined by the following: hirsutism score > 8 (Ferriman-Gallwey), amenorrhoea (no menses for 3 months), or oligomenorrhoea (menstrual cycles > 45 day); and high circulating levels of androstenedione or testosterone in the follicular phase (day 3 to 7) or after 2 months of amenorrhoea **Exclusion criteria of the trial** • Evidence of anaemia • Thyroid dysfunction • Bleeding disorder • Cushing syndrome • Hyperprolactinaemia • Glucose intolerance; diabetes mellitus • Late-onset adrenal hyperplasia • Abnormal electrolytes • Abnormal screening of liver or kidney function • Use of medication affecting gonadal or adrenal function, or carbohydrate or lipid metabolism • Pregnancy Randomised N = 34 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: EE-CPA group 23.0 (0.8), PioFluMet group 22.6 (0.6) F-G score: EE-CPA group 13.5 (0.9), PioFluMet group 14.0 (0.9) Acne score: EE-CPA group 2.2 (0.2), PioFluMet group 2.3 (0.2) SHBG (nmol/L): EE-CPA group 23.0 (3), PioFluMet group 28 (3) Testosterone (ng/dl): EE-CPA group 58 (7), PioFluMet group 63 (7) Androstenedione (ng/dl): EE-CPA group 455 (32), PioFluMet group 474 (44) DHEAS (µg/dl): EE-CPA group 283 (32), PioFluMet group 287 (29)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (17) **Comparator** • Pioglitazone 7.5 mg + flutamide 62.5 mg + metformin 850 mg for 6 months (17)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Weight, height, BMI * 2. Ferriman-Gallwey score * 3. Acne score; Leeds grading scale (O'Brien 1998) * 4. Glucose, insulin, lipid profile 5. SHBG, testosterone, androstenedione, DHEAS * 6. C-reactive protein, IGF-1, leptin, high molecular weight adiponectin, and follistatin, blood count and liver and kidney function

	7. Carotid intima-media thickness 8. Body composition (dual-energy x-ray absorptiometry) and abdominal fat distribution (MRI) 9. Gene expression in longitudinal biopsies of subcutaneous adipose tissue at the abdominal level (RT-PCR) * Denotes outcomes prespecified for this review
Notes	All of the participants in this study are included in 4 further studies (see under primary reference)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 3631): "Randomization was performed with the SealedEnvelope program (Sealed Envelope Ltd., London, UK) (http://www.SealedEnvelope.com), using random permuted blocks with strata for age and BMI." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 3631): "Randomization was performed with the SealedEnvelope program (Sealed Envelope Ltd., London, UK) (http://www. SealedEnvelope.com), using random permuted blocks with strata for age and BMI." Comment: form of central allocation, probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 3630): "...open-label ..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 3630-2): "...open-label..." and "Longitudinal ultrasound scans of the carotid arteries were obtained by the same investigator (blinded to treatment allocation" and "All scans were performed by the same operator, and all images were analyzed by the same radiologist (both blinded to treatment allocation)." Comment: although the measurement was blinded for certain outcomes, for the remaining outcomes the measurement is likely to be influenced by the lack of blinding

Ibáñez 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Intention-to-treat analysis Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Iraji 2005

Methods	Randomised, placebo-controlled, within-participant trial Setting Dermatology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran Date of study Not reported. Duration of the intervention 6 months
Participants	N = 35 Age range = 19 to 40 years **Inclusion criteria of the trial** • Idiopathic hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 35 Withdrawals/losses to follow-up • 5/35 (14%); due to no effect Baseline data Nothing reported
Interventions	**Intervention** • Finasteride cream 0.5% b.i.d. for 6 months **Comparator** • Placebo cream b.i.d. for 6 months
Outcomes	Assessments (4): baseline, month 2, 4, and 6 **Outcomes of the trial** (as reported) 1. Hair density; number of terminal hairs in a 1 cm^2 area * 2. The subjective view of the effect of the medication; by questioning about the number of times the patient had shaved or clipped hairs per week *

	3. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 337): "were chosen randomly and blindly" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 337-8): "...blindly..." "The final cream contained 0.5% finasteride. 30g of mixture was put into a tube. The placebo cream consisted of the Dermabase alone in the same size and type of tube. No difference in color or texture was evident between the placebo and medication containing creams" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/35 (14%) dropped out due to lack of effect. Per-protocol analysis Comment: moderate drop-out rate with

		per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Jackson 2007

Methods	2 randomised, double-blind, vehicle-controlled trials Setting Multi-centre (18) in the US (17) and Spain (1) Date of study Not reported. Duration of intervention 24 weeks with 8 weeks follow-up
Participants	N = 594 Age range = 18 to 83 years **Inclusion criteria of the trial** • Women of at least 16 years of age with a clinical diagnosis of facial hirsutism • An average hair density of at least 5 hairs per cm^2 on both the chin and upper lip as assessed by video image analysis • Customary frequency of hair removal of at least twice per week • Good general health • A negative serum or urine pregnancy test for women of child-bearing age • A score of at least 20 on a VAS ranging from 0 (not bothered) to 100 (extremely bothered) for the question: "How much are you bothered by your facial hair?" **Exclusion criteria of the trial** • Not reported Randomised N = 594 Withdrawals/losses to follow-up • 86/594 (14%); 10% in eflornithine group and 13% in vehicle group (no exact numbers) Baseline data No data regarding hirsutism score or hormone levels
Interventions	**Intervention** • Eflornithine HCl 13.9% cream b.i.d. for 24 weeks with 8 weeks follow-up (335 = N that completed the study) **Comparator** • Vehicle b.i.d. for 24 weeks with 8 weeks follow-up (173 = N that completed the study) During the study, subjects were permitted to continue their normal hair removal method;

	however, shaving and cutting were not permitted within 24 hours of 1st day of a scheduled study visit, plucking within 48 hours, or bleaching within 1 week of the first day of a scheduled visit
Outcomes	Assessments (7): baseline, weeks 2, 4, 8, 16, 24, and 32 **Outcomes of the trial** (as reported) 1. Physician's Global Assessment (photographic assessment); 4-point Likert scale * 2. Patient reported outcome (PRO); ESTEEM (Exchanges of affection, Social interactions, Time spent removing facial hair, Encountering new people, Engaging in work or school, Minimizing overall bother with facial hair) * * Denotes outcomes prespecified for this review
Notes	Unclear how many started in each group, data represent only those that finished. This is the same study as Wolf 2007, but partly covering other outcomes. The number of participants completing the study are not consistent in the 2 papers ESTEEM is a modification of the Bother Assessment in Skin Conditions (BASC) scale (developed and used in a study on the impact of hyperpigmentation) and consists of 6 questions to cover the discomfort felt in four social situations and bother due to removing facial hair. Each question elicits responses on a visual analogue scale (VAS), in which 0 is 'not bothered' and 100 is 'extremely bothered' (Caro 1996)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 977): "Subjects were randomized to receive..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication (quote): "Subjects were assigned treatment by a computer-generated randomization schedule restricted to ensure distribution of eflornithine 15% cream and its vehicle in a 2:1 ratio, respectively, within each investigational site." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported After e-mail communication (quote):

		"Subject numbers and numbers identifying study medication containers corresponded directly." and " The second panel of the tear-off part of the label was a sealed envelope concealing the identity and lot number of the treatments. These tear-off portions were to be affixed to the subjects CRFs and opened only in the case of a medical emergency in which the investigator had determined that the information was absolutely necessary, i.e., that it would alter the subjects immediate management." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 976): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication (quote): "Blinding of the eflornithine 15% cream and its vehicle was assured by the fact that both study medications were packaged in identically appearing 15g plastic tubes bearing three-panel, two-part double-blind labels. Labels affixed to the tubes (the only label to which subjects had access) contained no evidence of the identity of the contents... Eflornithine 15% cream and its vehicle were matching cream formulations and it was not considered possible to differentiate one treatment from the other solely by tactile or visual evaluation. The protocol for this study specified that dispensing of study medications at the investigational site was to be done by a staff member who was not responsible for conducting any of the clinical evaluations. Therefore, the chances of the investigator equating a particular level of response with what he/she considered to be a particular treatment was minimal."

		Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 976): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail contact (quote): see above Outcomes were investigator-assessed as well as participant-assessed (menstruation). Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	86/594 (14%); 10% in eflornithine group and 13% in vehicle group (no exact numbers). Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 976 and 981): "From the Bristol Myers-Squibb Pharmaceutical Research Institute..." and "This work was supported in part by a grant from Bristol-Myers Squibb" Comment: a potential risk of bias cannot be excluded

Javidnia 2003

Methods	Randomised, double-blind, active and placebo-controlled trial Setting Department of Dermatology, Shaheed Faghihi hospital, Shiraz, Iran Date of study Not reported. Duration of intervention 12 weeks
Participants	N = 45 Mean age = 29 years **Inclusion criteria of the trial** • Mild to moderate forms of idiopathic hirsutism localised to the face • Normal androgen levels **Exclusion criteria of the trial** • PCOS Randomised N = 45 Withdrawals/losses to follow-up • 7/45 (16%); 4/15 in fennel 1% group, 0/15 in fennel 2% group, 3/15 in vehicle group • Reasons unreported Baseline data Area involved Chin: fennel 1% group 7/11, fennel 2% group 10/15, vehicle 6/15 Cheek: fennel 1% group 2/11, fennel 2% group 7/15, vehicle 3/15 Upper lip: fennel 1% group 2/11, fennel 2% group 4/15, vehicle 3/15
Interventions	**Intervention** • Fennel 1% cream b.i.d. for 12 weeks (15) **Comparator 1** • Fennel 2% cream b.i.d. for 12 weeks (15) **Comparator 2** • Vehicle cream b.i.d. for 12 weeks (15)
Outcomes	Assessments (4): baseline, week 4, 8, and 12 **Outcomes of the trial** (as reported) 1. Patient's subjective satisfaction * 2. Density (hair diameter) and hair growth * *Denotes outcomes prespecified for this review
Notes	Individual participant data are reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 456): "...randomly assigned.." . Comment: insufficient detail was reported

		about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 456): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 456): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/45 (16%); 4/15 in fennel 1% group, 0/15 in fennel 2% group, 3/15 in vehicle group. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	High risk	Patient's subjective satisfaction and hair growth rate were prespecified outcomes but not reported Comment: we judged this as at a high risk of bias
Other bias	Low risk	Quote (page 458): "This project was undertaken by the financial support of Shiraz University of Medical Sciences" Comment: we judged this as at a low risk of bias

Jedel 2011

Methods	Randomised controlled trial Setting Sahlgrenska University Hospital and Sahlgrenska Academy at University of Göteborg, Sweden Date of study Recruitment between November 2005 and January 2008. Duration of intervention 16 weeks with 16 weeks follow-up
Participants	N = 84 Mean age = 30 years **Inclusion criteria of the trial** • PCOS, ultrasound-verified polycystic ovaries with 12 follicles 2 mm to 9 mm and/or an ovarian volume of 10 ml in one or both ovaries, together with either oligo/amenorrhoea and/or clinical signs of hyperandrogenism (hirsutism or acne) • Hirsutism was defined as a Ferriman-Gallwey score of 8, presence of acne was defined by positive response to the question "Do you have acne?" **Exclusion criteria of the trial** • Age > 38 years • Any pharmacological treatment within 12 weeks • Breast feeding within 24 weeks of entering the study • Cardiovascular disease • Diabetes mellitus • Endocrine or neoplastic causes of hyperandrogenaemia, including androgen-secreting tumours, Cushing's syndrome, congenital adrenal hyperplasia, and hyperprolactinaemia Randomised N = 84 Withdrawals/losses to follow-up • 25/84 (30%); 9/33 in acupuncture group, 12/34 in exercise group, 4/17 in no intervention group • Moved from area; 3/33 in acupuncture group, 0/34 in exercise group, 1/17 in no intervention group • Personal reasons; 3/33 in acupuncture group, 8/34 in exercise group, 3/17 in no intervention group • Pregnancy; 0/33 in acupuncture group, 1/34 in exercise group, 0/17 in no intervention group • Diet; 1/33 in acupuncture group, 0/34 in exercise group, 0/17 in no intervention group • Pharmacological treatment; 2/33 in acupuncture group, 2/34 in exercise group, 0/17 in no intervention group • Other disease; 0/33 in acupuncture group, 1/34 in exercise group, 1/17 in no intervention group Baseline data (mean (SD)) BMI: acupuncture group 29.1 (8.83), exercise group 27.7 (6.44), no intervention group 26.8 (5.56) F-G score: acupuncture group 12.1 (8.06), exercise group 13.1 (7.99), no intervention group 10.1 (5.20) Acne yes/no: acupuncture group 19/28, exercise group 15/29, no intervention group 11/15

	Testosterone (ng/ml): acupuncture group 0.40 (0.16), exercise group 0.45 (0.19), no intervention group 0.47 (0.21) Free testosterone (pg/ml): acupuncture group 7.27 (4.05), exercise group 7.81 (3.74), no intervention group 7.58 (4.04) DHEAS (µg/ml): acupuncture group 1.72 (0.67), exercise group 1.93 (0.99), no intervention group 1.70 (0.67) SHBG (nmol/L): acupuncture group 42.4 (25.3), exercise group 40.5 (18.8), no intervention group 45.3 (18.96)
Interventions	**Intervention** • Low-frequency electro-acupuncture, 14 treatments over 16 weeks (33) **Comparator 1** • Regular exercise at least 3 times a week for 30 minutes for 16 weeks (34) **Comparator 2** • No active intervention (17) All participants received general information concerning the benefits of regular physical exercise and were instructed to complete a physical exercise diary during weeks 1 to 32 of the study
Outcomes	Assessments (3): baseline, week 16 and 32 **Outcomes of the trial** (as reported) 1. BMI * 2. Ferriman-Gallwey score * 3. Presence of acne * 4. Serum DHEAS, androstenedione, testosterone, free testosterone, dihydrotestosterone, estrone, estradiol, LH, FSH, SHBG * 5. Menstrual bleeding * 6. Maximum oxygen uptake *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page E38): "...were randomly allocated in a 2:2:1 ratio..." and "To ensure equal proportions of age and body mass index (BMI) in each study arm, randomization was stratified by those variables. Computer-generated randomization within each stratum was conducted using permuted blocks of five and was concealed

		until interventions were assigned" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not feasible Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not feasible Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	25/84 (30%); 9/33 in acupuncture group, 12/34 in exercise group, 4/17 in no intervention group. Reasons reported, per-protocol analysis Comment: high drop-out rate with per-protocol analysis represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 44): "This study was financed by grants from the Osher Center for Integrative Medicine, the Swedish Medical Research Council ..., the Novo Nordisk Foundation, Wilhelm and Martina Lundgrens' Science Fund, the Hjalmar Svensson Foundation, the Tore Nilson Foundation, the Åke Wiberg Foundation, the Adlerbert Research Foundation, the Ekhaga Foundation, and the Swedish Federal Government Under Letters of Understanding Agreement of Medical Education ... and the Regional Research and Development Agreement ...)."

		Comment: we judged this as at a low risk of bias

Kaiser 1984

Methods	Randomised, active-controlled trial Setting Department of Gynecology and Endocrinology, Stiftung Deutsche Klinik für Diagnostik GmbH, Wiesbaden, Germany Date of study Not reported. Duration of intervention 12 months
Participants	N = 80 Mean age = 30 years **Inclusion criteria of the trial** • Women 19 to 47 years with acne, seborrhoea, diffuse hair loss, and/or hirsutism **Exclusion criteria of the trial** • Androgen-producing tumour Randomised N = 80 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data Duration of the virilisation symptoms 8 to 9 years
Interventions	**Intervention** • OCP (ethinyl estradiol 30 μg + chlormadinone acetate 2 mg) for 12 months (41) **Comparator** • OCP (norethisterone 1 mg and mestranol 50 µg) for 12 months (39)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Effect on acne, seborrhoea, alopecia, and/or hirsutism; 3-point Likert scale * 2. Adverse events * * Denotes outcomes prespecified for this review
Notes	Report of 2 studies. First study, all participants received the intervention, in the 2nd study participants were randomised. No wash-out period between the 2 studies. Unclear how many women were hirsute. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 652): "...erfolgte nach eine Randomisierungsplan..."

Kaiser 1984 (*Continued*)

		Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Kaya 2010

Methods	Randomised, active-controlled trial Setting Ufuk University, Faculty of Medicine, Department of Obstetrics and Gynecology, Ufuk, Turkey Date of study Not reported. Duration of intervention 3 months
Participants	N = 80 assessed for eligibility, 64 randomised Mean age = 27 years **Inclusion criteria of the trial**

	• PCOS • PCOS diagnosis based on Rotterdam Criteria PCOS 2004 • Hirsutism was determined by a modified Ferriman-Gallwey score > 7 **Exclusion criteria of the trial** • Nonclassic adrenal 21-hydroxylase deficiency • Hyperprolactinaemia • Androgen-secreting tumours • Diabetes • Congenital adrenal hyperplasia • Thyroid disorders • Cushing's syndrome • Infectious diseases • Hypertension • Smoking • Family history of cardiovascular disease • Hepatic or renal dysfunction Randomised N = 64 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SEM)) BMI: atorvastatin group 24.0 (5.4), simvastatin group 24.2 (4.2) F-G score: atorvastatin group 10 (2), simvastatin group 9 (4) Waist/hip ratio: atorvastatin group 0.79 (0.09), simvastatin group 0.78 (0.07) DHEAS (μg/dl): atorvastatin group 365.6 (84.6), simvastatin group 326.4 (71.5) Testosterone (ng/ml): atorvastatin group 0.87 (0.35), simvastatin group 0.89 (0.46)
Interventions	**Intervention** • Atorvastatin 20 mg once a day for 3 months (32) **Comparator** • Simvastatin 20 mg once a day for 3 months (32)
Outcomes	Assessments (2): baseline and month 3 **Outcomes of the trial** (as reported) 1. BMI, waist/hip ratio * 2. FSH, LH, prolactin, total testosterone, DHEAS, 17-OH-progesterone, TSH, SHBG, lipid profile and basal insulin levels * 3. Oral glucose tolerance test 4. HOMA-IR 5. FAI 6. Serum malondialdehyde, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides * Denotes outcomes prespecified for this review
Notes	-
Risk of bias	

Kaya 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 162): "... were randomized to two groups by an allocation sequence generated from a random number table" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 162): "...assigned through consecutively numbered opaque, sealed envelopes." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Kelekci 2012

Methods	Randomised, active-controlled trial Setting Dermatology Clinic and Department of Obstetrics and Gynecology, Numune Education and Research Hospital, Seyhan Practice Center, Adana, Turkey Date of study August 2006 until May 2009. Duration of intervention 6 months
Participants	N = 296 assessed for eligibility, 166 randomised Mean age = 23 years **Inclusion criteria of the trial** • Nulligravid women 17 to 35 years with moderate-to-severe hirsutism • Not pregnant and not will to conceive **Exclusion criteria of the trial** • Smoking • Thyroid disease • Breast or endometrium cancer • Previous treatment for hirsutism • Active liver disease • History of thromboembolic disease • Diabetes, adrenal disorders, hyperprolactinaemia, late-onset congenital adrenal hyperplasia Randomised N = 166 Withdrawals/losses to follow-up • 22/166 (13%); 10/55 EE/DRSP + CPA group, 11/55 EE/DRSP + spironolactone group, 11/56 EE/CPA + CPA • Cost and fear of weight gain; 4/55 EE/DRSP + CPA group, 3/55 EE/DRSP + spironolactone group, 4/56 EE/CPA + CPA • Lost to follow-up; 6/55 EE/DRSP + CPA group, 8/55 EE/DRSP + spironolactone group, 7/56 EE/CPA + CPA Baseline data (mean (SD)) Modified F-G score: EE/DRSP + CPA group 16.58 (6.45), EE/DRSP + spironolactone group 13.75 (5.25), EE/CPA + CPA 14.04 (5.47) Testosterone (ng/ml): EE/DRSP + CPA group 0.87 (0.20), EE/DRSP + spironolactone group 0.85 (0.17), EE/CPA + CPA 0.79 (0.23) DHEAS (µg/ml): EE/DRSP + CPA group 214.56 (64.60), EE/DRSP + spironolactone group 199.94 (40.83), EE/CPA + CPA 189.72 (42.21)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) + 100 mg cyproterone acetate for 6 months (55) **Comparator 1** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) + 100 mg spironolactone for 6 months (55) **Comparator 1** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + 100 mg cyproterone acetate for 6 months (56)

Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Serum total testosterone, DHEAS, and 17-OH progesterone * 3. Change in ovarian morphology 4. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 178): "According to a computer-generated randomization table, women were randomly assigned to three treatment groups..." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 178): "Group allocation was predetermined and placed in consecutively numbered opaque, sealed envelopes. The next consecutive envelope was drawn after the patient consented to randomization." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 178): "Randomization was carried out blindly with respect to the patient's clinical features while patients were not blind to treatment regimens." and "Hirsutism was always evaluated by the same blinded physician using the mFGS" Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Kelekci 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 178): "Randomization was carried out blindly with respect to the patient's clinical features while patients were not blind to treatment regimens." and "Hirsutism was always evaluated by the same blinded physician using the mFGS" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	22/166 (13%); 10/55 EE/DRSP + CPA group, 11/55 EE/DRSP + spironolactone group, 11/56 EE/CPA + CPA. Reasons reported. Per-protocol analysis Comment: moderate drop-out rate with per-protocol analysis represents an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Kelly 2002

Methods	Randomised, double-blind, placebo-controlled, cross-over trial Setting Stobhill Hospital, North Glasgow University NHS Trust, Glasgow, UK Date of study Not reported. Duration of intervention 2 phases of 6 months with 2 months wash-out in between
Participants	N = 16 Mean age = not reported **Inclusion criteria of the trial** • PCOS with hirsutism • PCOS defined as androgen excess (total testosterone > 3.6 nmol/L or a free androgen index (FAI) $\geq$ 9%) with ovulatory dysfunction (less than 6 menstrual cycles per year) once specific disorders, such as adult onset congenital adrenal hyperplasia, hyperprolactinaemia and androgen-secreting neoplasia had been excluded

	• Hirsutism defined as Ferriman-Gallwey score > 8 • Previously noted no improvement in hirsutism following 6 months of OCP (ethinyl estradiol 35 mg, cyproterone acetate 2 mg) **Exclusion criteria of the trial** • Treatment for hirsutism Randomised N = 16 Withdrawals/losses to follow-up • 6/16 (38%); 3 for non-compliance, 3 for no effect (in first phase on placebo) Baseline data (mean (SEM)) F-G score: 17.7 (1.4)
Interventions	**Intervention** • Metformin 500 mg at start up to 3 times a day for 6 months **Comparator** • Placebo for 6 months After 6 months, 2 months wash-out, and then cross-over for another 6 months
Outcomes	Assessments (8): baseline, month 2, 4, 6, 8, 10, 12, and 14 **Outcomes of the trial** (as reported) 1. Menstrual history * 2. Weight, waist-hip ratio, and blood pressure 3. Compliance 4. Hair growth; averaging the length of up to 5 hairs removed from the chin * 5. Ferriman-Gallwey score * 6. Participant's self assessment; 5-point Likert scale * 7. Glucose, gonadotrophins, total testosterone, DHEAS, androstenedione, SHBG, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides * * Denotes outcomes prespecified for this review
Notes	No end of first-phase data, nor baseline data for 2nd phase. See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 147): "The pharmacist randomised the subjects by coin tossing in batches of four in a four square design to metformin or an identical placebo (BMS, Hounslow, UK)" Comment: probably done

Kelly 2002 (*Continued*)

Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 147): "double-blind" and "to metformin or an identical placebo..." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	6/16 (38%); 3 for non-compliance, 3 for no effect (in first phase on placebo) Comment: high drop-out rate with per-protocol analysis represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 221): "We would also like to thank BMS (Hounslow, UK) for supplying metformin and placebo preparations." Comment: we judged this as at a low risk of bias

Kjøtrød 2004

Methods	Randomised, double-blind, placebo-controlled study Setting IVF Unit, Department of Obstetrics and Gynaecology, Trondheim University Hospital, Trondheim, Norway Date of study Recruitment between January 2001 and June 2002. Duration of intervention 16 weeks
Participants	N = 73 Mean age = 30 years **Inclusion criteria of the trial**

	• Infertile women with PCOS • PCOS; polycystic with at least 10 follicles 2 ± 10 mm in diameter, and increased density and area of ovarian stroma determined by the use of ultrasound; oligo/amenorrhoea; one of the following 5 criteria had to be fulfilled: testosterone > 2.0 nmol/L, SHBG) < 30 nmol/L, LH/FSH ratio > 2, fasting insulin C-peptide > 1.0 nmol/L or hirsutism • Hirsutism was defined as the need to remove unwanted facial hair at least once a week **Exclusion criteria of the trial** • Diabetes mellitus • Renal insufficiency (creatinine > 130 mmol/L) • Liver disease (alanine aminotransferase > 80 U/L) • Treatment with oral glucocorticoids • Hyperprolactinaemia • Abnormal thyroid function tests • Congenital adrenal hyperplasia • Androgen-secreting tumours Randomised N = 73 Withdrawals/losses to follow-up • 10/74 (14%); 2/15 in normal weight placebo group, 4/18 in normal weight metformin group, 2/21 in obese placebo group, 2/19 in obese metformin group • Economic reasons; 0/15 in normal weight placebo group, 0/18 in normal weight metformin group, 2/21 in obese placebo group, 2/19 in obese metformin group • Pregnancy; 2/15 in normal weight placebo group, 4/18 in normal weight metformin group, 0/21 in obese placebo group, 0/19 in obese metformin group Baseline data N with hirsutism: 10/31 in metformin group, 13/32 in placebo group N with testosterone > 2 nmol/L: 22/31 in metformin group, 19/32 in placebo group N with SHBG < 30 nmol/L: 20/31 in metformin group, 18/32 in placebo group
Interventions	**Intervention** • Metformin 500 mg b.i.d. for 16 weeks (37) **Comparator** • Placebo b.i.d. for 16 weeks (36) Treatments ended on the day of HCG injection for IVF stimulation
Outcomes	Assessments (2): baseline and week 16 **Outcomes of the trial** (as reported) 1. Total number of days of FSH stimulation and serum estradiol on the day of HCG injection 2. Number of oocytes 3. Total gonadotrophin dose used 4. Fertilisation rates, embryo quality, pregnancy rates, clinical pregnancy rate, and live birth rates * Denotes outcomes prespecified for this review
Notes	Only 37% of women were hirsute and none of our outcomes were assessed. No separate data for hirsute women. See Table 3

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 1316): "Randomization was performed by our hospital pharmacy; it was performed in blocks of four and stratified according to BMI <28 kg/m2 or BMI >28 kg/m2." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1316): "Randomization codes were kept in the pharmacy until the last patient had finished the IVF procedure." Pharmacy controlled randomisation Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1316): "Patients were treated with identical capsules of metformin or placebo" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/74 (14%); 2/15 in normal weight placebo group, 4/18 in normal weight metformin group, 2/21 in obese placebo group, 2/19 in obese metformin group Comment: as 6 got pregnant, which was a desired outcome, the number of real drop-outs (N = 4), balanced between the groups, is low. We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Kjøtrød 2004 (*Continued*)

Other bias	Low risk	Quote (page 1321): "We gratefully thank Weifa AS, Norway, for supplying the metformin used free of charge, and Organon AS, Norway, for supporting gonadotrophin for the last 15 cycles (after public financing of IVF changed in Norway on January 1, 2002)." Comment: we judged this as at a low risk of bias

Kriplani 2009

Methods	Randomised, active-controlled trial Setting Outpatient Gynecology endocrine clinic, All India Institute of Medical Sciences, New Delhi, India Date of study Not reported. Duration of intervention 12 months
Participants	N = 120 Mean age = 23 years **Inclusion criteria** • Hirsutism based on PCOS (Rotterdam Criteria PCOS 2004) and idiopathic hirsutism • Hirsutism score ≥ 8 (modified Ferriman-Gallwey score) • Age between 16 to 40 years **Exclusion criteria** • Androgen-secreting tumours of ovarian or adrenal origin • Cushing syndrome • Thyroid dysfunction • 21-hydroxylase deficiency • Hyperprolactinaemia • Cliteromegaly or other evidence of virilism • Intersex patients • < 6 months on medication that are known to affect pituitary-gonadal function Randomised N = 60 Withdrawals/losses to follow-up • 8/120 (6.7%); 5/60 in OCP + spironolactone group for side effects, 3/60 in OCP + finasteride group also for side effects Baseline data (mean (SD)) BMI: OCP + spironolactone group 24.2 (6.1), OCP + finasteride group 22.5 (4.2) Modified F-G score: OCP + spironolactone group 11.4 (2.8), OCP + finasteride group 11.1 (2.4) Acne present: OCP + spironolactone group 20, OCP + finasteride group 25 Total testosterone (ng/ml): OCP + spironolactone group 1.3 (1.3), OCP + finasteride group 1.1 (1) DHEAS (µg/dl): OCP + spironolactone group 212.4 (117.6), OCP + finasteride group

	219.5 (126.3)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + spironolactone 100 mg for 12 months (60) **Comparator** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + finasteride 5 mg for 12 months (60)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Adverse events * 3. Acne score (per Indian system) * 4. LH, FSH, TSH, prolactin, total testosterone, DHEAS, 17-hydroxyprogesterone * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 237): "The choice of treatment for each patient was made using a computerized randomization number table." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding

Incomplete outcome data (attrition bias) All outcomes	Low risk	8/120 (6.7%); 5/60 in OCP + spironolactone group for side effects, 3/60 in OCP + finasteride group also for side effects Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 240): "We are thankful to the Indian Council of Medical Research, New Delhi, India for funding and supporting this project (ID NO: 2007-00940)." Comment: we judged this as at a low risk of bias

Kriplani 2010

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India Date of study Not reported. Duration of intervention 6 months with follow-up at 12 months
Participants	N = 73 assessed for eligibility, 60 randomised Mean age = 23 years **Inclusion criteria of the trial** • PCOS according to Rotterdam Criteria PCOS 2004 **Exclusion criteria of the trial** • Hypothyroidism • Hyperprolactinaemia • History of exogenous hormonal agent within past 6 months • Smoking • Alcohol • Recent history of surgical treatment for PCOS • Contraindications to combined oral contraceptives • Associated renal or adrenal insufficiency on drugs that increase serum potassium (ACE inhibitors, AT II blockers) Randomised N = 60 Withdrawals/losses to follow-up • 2/60 (3%); 1/30 in EE/DRSP group, 1/30 in EE/desogestrel group • Jaundice; 1/30 in EE/DRSP group, 0/30 in EE/desogestrel group

	• Lower limb pain; 0/30 in EE/DRSP group, 1/30 in EE/desogestrel group Baseline data Hirsutism: 5/30 in EE/DRSP group and 4/30 in EE/desogestrel Acne: 10/30 in EE/DRSP group and 10/30 in EE/desogestrel Obese (BMI > 25 kg/m^2): 19/30 in EE/DRSP group and 20/30 in EE/desogestrel
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 6 months (30) **Comparator** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 6 months (30)
Outcomes	Assessments (6): baseline, month 1, 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Acne scoring * 3. BMI * 4. Haemoglobin, lipid profile, glucose, insulin, FSH, LH, TSH, prolactin, testosterone, SHBG, DHEAS, 17-OH progesterone * 5. Ultrasound of the pelvis for features of PCOS 6. Adverse effects * * Denotes outcomes prespecified for this review
Notes	Minority had hirsutism

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 140): "...using a computer-generated randomization table into two groups..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/60 (3%); 1/30 in EE/DRSP group, 1/30 in EE/desogestrel group, reasons reported. Per-protocol analysis Comment: low and balanced number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Lachnit-Fixson 1977

Methods	Randomised, double-blind, active-controlled trial Setting Multi-centre in Germany and Austria Date of study Not reported. Duration of intervention 6 to 12 months
Participants	N = 88 Mean age = 29 years **Inclusion criteria of the trial** • Participants with acne, seborrhoea, and/or hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 88 Withdrawals/losses to follow-up • Not clear and duration of therapy variable Baseline data Nothing reported
Interventions	**Intervention** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) for 6 to 12 months (37) **Comparator** • OCP (ethinyl estradiol 50 µg + D-norgestrel 0.25 mg) for 6 to 12 months (51)

Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Effect on acne, seborrhoea, and/or hirsutism; 5-point Likert scale * * Denotes outcomes prespecified for this review
Notes	Unclear how many women were hirsute and no precise data on the effect on hirsutism (only reported as no difference between the treatment groups). See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page1923): "...durch Randomisierung..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1923): "...doppelblind..." and "äußerlich identisch..." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many dropped out as study duration was variable. Appears to be 4 in the active treatment group and 11 in the control group that failed to complete 6 months treatment

Lachnit-Fixson 1977 (*Continued*)

		Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Principal investigator was employed by Schering AG, the manufacturer of the OCPs Comment: a potential risk of bias cannot be excluded

Ladson 2011

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Obstetrics and Gynecology, Meharry Medical College, Nashville, Tennessee and Department of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, Pennsylvania, US Date of study 2004 until 2007. Duration of intervention 6 months
Participants	N = 114 Mean age = 29 years **Inclusion criteria of the trial** • PCOS according to the 1990 National Institutes of Health/National Institute of Child Health and Human Development PCOS diagnostic criteria (Zawadski 1992); chronic anovulation, defined as spontaneous intermenstrual periods of ≥ 45 days or a total of ≤ 8 menses per year, and hyperandrogenism defined as an elevated total testosterone (> 50 ng/dl) or a free androgen index (ratio of testosterone/SHBG (100)) > 1.5 **Exclusion criteria of the trial** • Other causes of anovulation and hyperandrogenism • Confounding medications (e.g. hormonal contraceptives, diabetic medications, etc.) Randomised N = 114 Withdrawals/losses to follow-up • 76/114 (67%); 33/55 in metformin group, 43/59 in placebo group • Side effects; 6/55 in metformin group, 0/59 in placebo group • Lost interest/unable to comply; 4/55 in metformin group, 7/59 in placebo group • Personal constraints/health issues; 8/55 in metformin group, 13/59 in placebo group • Pregnancy; 0/55 in metformin group, 4/59 in placebo group • Lost to follow-up; 15/55 in metformin group, 19/59 in placebo group

	Baseline data (mean (SD)) BMI: metformin group 38.0 (7.8), placebo group 38.3 (8.0) F-G score: metformin group 17.7 (8.3), placebo group 19.1 (8.9) Acne count: metformin group 4.4 (7.4), placebo group 2.6 (4.1) Testosterone (ng/dl): metformin group 73.6 (36.9), placebo group 77.3 (36.9) SHBG (nmol/L); metformin group 28.1 (25.4), placebo group 26.5 (12.9)
Interventions	**Intervention** • Metformin 500 mg, 4 capsules a day (55) **Comparator** • Placebo capsules, 4 capsules a day (59) All participants received a combined intervention of diet and exercise with the goal of achieving an average weight loss of ≥ 7% of initial body weight over 6 months with a prescription of 150 minutes/week exercise combined with a low-calorie diet
Outcomes	Assessments (7): baseline, and then every month until end of study **Outcomes of the trial** (as reported) 1. Ovulation rate; pregnanediol-3 alpha-glucuronide in urine 2. Testosterone levels * 3. Ferriman-Gallwey score, acne lesion counting * 4. Fitness level 5. Dual-energy x-ray absorptiometry 6. LH, FSH, DHEAS, SHBG * 7. OGTT, glucose, insulin 8. Ultrasound of pelvis 9. PCOS quality of life survey (Guyatt 2004) * 10. Adverse events * *Denotes outcomes prespecified for this review
Notes	Drop-out rate 67%. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1059): "... Subjects were randomized in a 1:1 allocation ratio to the two treatment arms...using a computer generated random number table using...permuted blocks and stratified by center and prior metformin exposure status after a baseline visit" Comment: probably done

Allocation concealment (selection bias)	Unclear risk	Quote (page 1059): "...The block schedule was blinded to the investigators and research subjects" Comment: the method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1060): "...Metformin hydrochloride was... formulated with the appropriate dose of drug into capsules with identical-appearing placebo capsules. Drug and placebo were packaged and labeled according to subject number by the Investigational Pharmacy laboratory in a double blind fashion" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were both participant and investigator assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	76/114 (67%); 33/55 in metformin group, 43/59 in placebo group, reasons reported. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Lakryc 2003

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Gynecology of the Federal University of Sao Paulo, Escola Paulista de Medicina, Sao Paulo, Brazil Date of study October 1997 until December 1999. Duration of intervention 6 months
Participants	N = 34 Mean age = not reported **Inclusion criteria of the trial** • Hirsute women (19 to 40 years) • PCOS as diagnosed by amenorrhoea or oligo menorrhoea (< 6 menstrual periods per year) or idiopathic hirsutism scored ≥ 8 **Exclusion criteria of the trial** • Lipid-lowering drugs • Antidiabetic medication • Hormonal drugs or contraception < 6 months prior to study entry • Cushing's syndrome • Late-onset 21-hydroxylase deficiency • Thyroid dysfunction • Hyperprolactinaemia • Androgen-secreting tumours • Diabetes mellitus • Renal or hepatic disease • Adrenal hirsutism • No previous treatment for hirsutism Randomised N = 34 Withdrawals/losses to follow-up • 10/34 (29%); 4/16 in finasteride group, 6/18 in placebo group • Pregnancy; 3/34 • Diarrhoea and nausea; 3/34 • Private reasons; 3/34 • Allergic symptoms; 1/34 Baseline data (mean (SEM)) BMI: PCOS group 24.3 (0.7), idiopathic hirsutism group 23.6 (0.6) F-G score: PCOS group 11.5 (0.8), idiopathic hirsutism group 12.6 (0.6) Free testosterone (nmol/L): PCOS group 14.6 (1.1), idiopathic hirsutism group 6.8 (0.5)
Interventions	**Intervention** • Finasteride 5 mg once a day for 6 months (12) **Comparator** • Placebo for 6 months (12)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Blood pressure

	3. Cardiac frequency 4. BMI * 5. Serum prolactin, 17OH progesterone, FSH, LH, total and free testosterone, DHEAS, androstenedione, dihydrotestosterone * 6. Subjective efficacy according to participants; 3-point Likert scale * 7. Transvaginal ultrasound (ovarian volume) 8. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 59): "... by a computerized random-number generator" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 59): "All patients received a numerical randomized envelope, which had a letter inside labeled no. 1 or no. 2 corresponding... During the study, the subjects and study personnel were not informed about the order of the treatments." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 59): "To avoid compromising the double-blind design the occurrence of side effects...was recorded by an independent gynecologist. The study drugs were packaged in 30-day flasks...The follow-up was conducted by a gynecologist who did not participate in the screening part of the study or the distribution of the drugs..." After e-mail communication: "The capsule of placebo was similar to the one of finasteride and the flask had only identification of XY (placebo) or YX (finasteride). The physicians and patients were blind to this information"

		Comment: the response from the investigators provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were both participant and investigator assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	10/34 (29%); 4/16 in finasteride group, 6/18 in placebo group, reasons reported. Per-protocol analysis Comment: the high drop-out rate (although balanced) with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Lam 2011

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Obstetrics and Gynecology, Prince of Wales Hospital, Hong Kong, People's Republic of China Date of study Inclusion from June 2004 until November 2006. Duration of intervention 12 months
Participants	N = 80 screened, 70 randomised Mean age = 26 years **Inclusion criteria of the trial** • Chinese women who were diagnosed with PCOS based on Rotterdam Criteria PCOS 2004 **Exclusion criteria of the trial** • Other causes of hyperandrogenaemia, i.e. adult onset congenital adrenal hyperplasia and Cushing's syndrome

	• Endometrial hyperplasia • Diabetes mellitus managed with oral hypoglycaemic agents or insulin treatment • Significant cardiovascular disease, hepatic or renal impairment • Corticosteroid therapy Randomised N = 70 Withdrawals/losses to follow-up • 16/70 (23%); 11/35 in rosiglitazone group, 5/35 in placebo group • Lost to follow-up; 8/35 in rosiglitazone group, 5/35 in placebo group • Withdrawn; 1/35 in rosiglitazone group, 0/35 in placebo group • Refused to continue; 2/35 in rosiglitazone group, 0/35 in placebo group Baseline data (mean (SD) or number (%)) BMI: rosiglitazone group 23.5 (5.2), placebo group 25.9 (5.6) F-G score: rosiglitazone group 6, placebo group 6; 8/35 in rosiglitazone group had score ≥ 11, 13/35 in placebo group had score ≥ 11 Waist/hip ratio: rosiglitazone group 0.80 (0.05), placebo group 0.81 (0.07) Amenorrhoea: rosiglitazone group 12/35, placebo group 20/35 Oligomenorrhoea: rosiglitazone group 21/35, placebo group 15/35 Acne score mild: rosiglitazone group 13 (37.1), placebo group 7 (20.0) Acne score moderate: rosiglitazone group 4 (11.4), placebo group 1 (2.9) Acne score severe: rosiglitazone group 2 (5.7), placebo group 2 (5.7)
Interventions	**Intervention** • Rosiglitazone 4 mg b.i.d. for 12 months (35) **Comparator** • Placebo b.i.d. for 12 months (35)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Menstrual status * 2. Hyperandrogenism (hirsutism and free testosterone) * 3. Insulin, glucose, lipid levels 4. BMI, waist/hip ratio * 5. Blood pressure 6. LH, FSH, total testosterone, SHBG * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 447): "...randomization generated in blocks of 10 by a computer program..." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 447): "...The "coding" of the placebo and the rosiglitazone in each bottle was kept only by the local pharmaceutical company and was concealed from the research team." and "Both the participants and the research team were blinded to the randomization codes, which were not broken until the completion of the study." Pharmacy-controlled randomisation Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 446-7): "Both the placebo and the rosiglitazone were encapsulated to appear the same and were packed into bottles with serially labeled study numbers" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	16/70 (23%); 11/35 in rosiglitazone group, 5/35 in placebo group, reasons reported. Per-protocol analysis Comment: the high and unbalanced drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Other bias	Low risk	The study appears to be free of other forms of bias

Lello 2008

Methods	Randomised, active-controlled trial Setting Endocrinological Gynecology and Pathophysiology of Menopause Unit, IRCCS-IDI, Rome, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 55 Mean age = 24 years **Inclusion criteria of the trial** • Women with hyperandrogenic manifestations (seborrhoea, acne, increased hair) and plasma hormonal hyperandrogenic features **Exclusion criteria of the trial** • Not reported Randomised N = 55 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SD)) BMI: EE/DRSP group 22.30 (2.60), EE/CMA group 22.24 (2.6) F-G score: EE/DRSP group 15.53 (2.03), EE/CMA group 15.41 (1.86) Acne score: EE/DRSP group 2.63 (0.39), EE/CMA group 2.56 (0.41) Androstenedione (ng/ml): EE/DRSP group 4.24 (0.54), EE/CMA group 4.17 (0.39) DHEAS (µg/ml): EE/DRSP group 3.134 (0.77), EE/CMA group 3.193 (0.75) Testosterone (nmol/L): EE/DRSP group 2.00 (0.23), EE/CMA group 2.05 (0.24) SHBG (nmol/L): EE/DRSP group 34.82 (6.10), EE/CMA group 35.27 (6.43)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 6 months (30) **Comparator** • OCP (ethinyl estradiol 30 µg + chlormadinone 2 mg) for 6 months (25)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Serum FSH, LH 17OH-progesterone, androstenedione, testosterone, DHEAS, SHBG * 2. Seborrhoea; MPA Cutometer 580® 3. Acne score; 4-point Likert scale (higher is worse) * 4. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 719): "Randomly, 30 patients. .." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 719): "...investigator was only one throughout the study and was always blinded to treatment..." The participants were not blinded Comment: the report did not provide sufficient detail about the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 719): "...investigator was only one throughout the study and was always blinded to treatment..." The participants were not blinded Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias

Lello 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Lemay 2006

Methods	Randomised, active-controlled trial Setting Départements d'Obstétrique-Gynécologie et de Biologie Médicale, Centre de Recherche, Hôpital St-François d'Assise, CHUQ, Université Laval, Québec, Canada Date of study Not reported. Duration of intervention 6 months
Participants	N = 50 assessed for eligibility, 28 randomised Mean age = 23 years **Inclusion criteria of the trial** • 18 to 45 years old with at least 2 previous menses and without menopausal symptoms • PCOS according to the presence of 2 out of 3 criteria: (i) oligomenorrhoea (< 8 uterine bleedings/year) or amenorrhoea (≤ 2 uterine bleedings/year); (ii) elevated levels of androgens (testosterone > 1.5 nmol/l and/or androstenedione > 10 nmol/l); and (iii) presence of micro-cysts (≥ 12 follicles measuring 2 mm to 9 mm in diameter) surrounding otherwise enlarged ovaries (> 10 cm^3) • A high fasting insulin (> 90 pmol/l) with normal glucose (< 6 mmol/l) indicative of insulin resistance **Exclusion criteria of the trial** • Actual desire for pregnancy • Hysterectomy, abnormal endometrial biopsy if abnormal bleeding in the last 6 months • Cushing's syndrome, congenital adrenal hyperplasia (17-OH progesterone > 10 nmol/L), excessive androgens suspicious of a tumour, prolactin levels > 50 μg/L • Severe renal or hepatic disease • Gastrointestinal condition interfering with drug absorption • Previous breast, uterus, ovary, or liver neoplasia • Previous use of a drug to lower glucose, lipid, or insulin or an oral contraceptive in the last 2 months • Previous use of diuretic, β-blocker, corticoid, hormonal replacement therapy in the last 3 months, depo-medroxyprogesterone acetate injection in the last year and a research drug in the last 2 months • Alcohol intake > 40 g/day and smoking > 10 cigarettes/day Randomised N = 28

	Withdrawals/losses to follow-up • 11/28 (39%); 5/15 in rosiglitazone group, 6/13 in EE/CPA group • Refused to continue; 3/15 in rosiglitazone group, 3/13 in EE/CPA group • Intolerance; 1/15 in rosiglitazone group, 2/13 in EE/CPA group • Unrelated to medication; 1/15 in rosiglitazone group, 1/13 in EE/CPA group Baseline data (mean (SD)) BMI: rosiglitazone group 34.6 (4.7), EE/CPA group 33.9 (4.6) F-G score: rosiglitazone group 16.7 (5.7), EE/CPA group 17.1 (2.0) Waist/hip ratio: rosiglitazone group 1.00 (0.03), EE/CPA group 0.98 (0.04) Baseline data (mean (SEM)) Testosterone (mmol/L): rosiglitazone group 2.29 (0.24), EE/CPA group 1.93 (0.25) Androstenedione (mmol/L): rosiglitazone group 12.2 (0.8), EE/CPA group 11.2 (1.0) DHEAS (pmol/L): rosiglitazone group 6.72 (1.00), EE/CPA group 7.37 (1.37) SHBG (mmol/L): rosiglitazone group 13.2 (1.5), EE/CPA group 13 (2)
Interventions	**Intervention** • Rosiglitazone 4 mg/day for 6 months (15) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (13) Admissible candidates were started on diet low in refined sugar for 4 months before randomisation to drug treatment. Subjects were also encouraged to exercise daily whenever possible
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Glucose, insulin, lipid profile, oral glucose tolerance test, HOMA, QUICKI 2. Compliance to diet and exercise 3. Adverse effects * 4. Ferriman-Gallwey score * 5. TSH, prolactin, FSH, LH, estradiol, progesterone, total testosterone, DHEAS, SHBG, androstenedione * 6. BMI, waist/hip ratio, blood pressure, and smoking and alcohol drinking habits * * Denotes outcomes prespecified for this review
Notes	The study continued after 6 months with a combination of the 2 treatments. Losses to follow-up in the EE + CPA group > 40 % (46.2 %). See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 122): "Computer generated allocation blocks of four to six subjects were used for randomization" Comment: probably done

Lemay 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	11/28 (39%); 5/15 in rosiglitazone group, 6/13 in EE/CPA group, reasons reported. Per-protocol analysis Comment: the high drop-out rate (although balanced) with per-protocol analysis represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 127): "Drugs were graciously supplied by Berlex Canada Inc. and GlaxoSmithKline Montreal, Québec, Canada." Comment: we judged this as at a low risk of bias

Levrier 1988

Methods	Randomised, active-controlled trial Setting Multi-centre in France Date of study Not reported. Duration of intervention 6 months
Participants	N = 69 Mean age = 24 years **Inclusion criteria of the trial**

	• 18 to 35 years with acne **Exclusion criteria of the trial** • Oral antibiotics < 1 month prior to study entry • OCP other than minipill Randomised N = 69 Withdrawals/losses to follow-up • 3/69 (4%); 1/30 in EE/desogestrel group, 2/39 in EE/CPA group • Adverse event; 1/30 in EE/desogestrel group, 1/39 in EE/CPA group • Lost to follow-up; 0/30 in EE/desogestrel group, 1/39 in EE/CPA group Baseline data Nothing reported
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 6 months (30) **Comparator** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) for 6 months (39)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Acne lesions; number * 2. Hirsutism on upper lip, preauricular and chin * 3. Serum total testosterone, SHBG * 4. Adverse events * *Denotes outcomes prespecified for this review
Notes	Only few of the women had additional hirsutism, unclear how many in each group as only some of the sites but not the number of participants are reported. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 574): "...randomisée..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported

Levrier 1988 (*Continued*)

		Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/69 (4%); 1/30 in EE/desogestrel group, 2/39 in EE/CPA group were lost to follow-up. Incomplete data 27 in EE/desogestrel group and 35 in EE/CPA group Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Lissak 1989

Methods	Randomised controlled trial Setting Department of Obstetrics and Gynecology, Carmel Hospital, Haifa, Israel Date of study Not reported. Duration of intervention 3 months
Participants	N = 20 Age range = 15 to 35 years **Inclusion criteria of the trial** • Moderate to severe hirsutism for at least 3 years **Exclusion criteria of the trial** • Hirsutism treatment < 6 months prior to study entry Randomised N = 20 Withdrawals/losses to follow-up • 3/20 (15%); 2/12 in cimetidine group, 1/8 in control group, did not show up for follow-up Baseline data

Lissak 1989 (*Continued*)

	10 women had hirsutism with ovarian source predominating, 4 of adrenal origin, 6 had idiopathic hirsutism
Interventions	**Intervention** • Cimetidine 300 mg 5 times a day for 3 months (12) **Comparator** • No treatment (8)
Outcomes	Assessments (4): baseline, month 1, 2, and 3 **Outcomes of the trial** (as reported) 1. Quantitative assessment of body hair * 2. Ferriman-Gallwey score * 3. Free thyroxine, adrenal corticotropic hormone, FSH, LH, prolactin, total testosterone, free testosterone, DHEA, DHEAS * 4. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 248): "... were randomised to treatment..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Lissak 1989 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/20 (15%); 2/12 in cimetidine group, 1/8 in control group, did not show up for follow-up. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 250): "The research was supported in part by a grant from Mr Beni Peled, President of Elscint Ltd., Haifa, Israel" Comment: we judged this as at a low risk of bias

Lucas 2001

Methods	Randomised, double-blind, placebo-controlled, within-participant trial Setting Down East Medical Associates, Morehead City, North Carolina, US Date of study Not reported. Duration of intervention 6 months
Participants	N = 8 Mean age = 39 years **Inclusion criteria of the trial** • Excessive facial hair with different severities and causes of hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 8 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SEM)) BMI: 36.5 (5.72) 4 had PCOS, 2 idiopathic hirsutism, 1 hypertrichosis, and 1 mild congenital adrenal hyperplasia

Lucas 2001 (*Continued*)

Interventions	**Intervention** • Finasteride (0.25%) cream b.i.d. for 6 months **Comparator** • Placebo cream b.i.d. for 6 months
Outcomes	Assessments (4): baseline, month, 2, 4, and 6 **Outcomes of the trial** (as reported) 1. Subjective view of effect; questioning about the numbers of times per week shaving/clipping * 2. Perception of differences between the 2 sides by participants * 3. Inquiries about hair removal techniques 4. Testosterone, DHEAS, prolactin, TSH * 5. Adverse events/tolerability * * Denotes outcomes prespecified for this review
Notes	2/8 had diagnosis that did not match our inclusion criteria. Individual patient data are provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 5): "... randomized and blinded..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 7): "... same size, and type of tube...cream labeled "R" on right side..."L" on left side...women and researcher were blinded to the identity of the cream in each of the tubes." Comment: the report provided sufficient

Lucas 2001 (*Continued*)

		detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by participants and investigators. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 9): "I thank...the local Merck & Co representative for the idea of the study..." Comment: we judged this as at a low risk of bias

Lumachi 2003

Methods	Randomised, active-controlled trial Setting Endocrine Surgery Unit, Department of Surgical and Gastroenterological Sciences, University of Padua, School of Medicine, Padova, Italy Date of study Not reported. Duration of intervention 12 months
Participants	N = 41 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute women Ferriman-Gallwey score $\geq$ 6 • Regular menstrual cycles of 21 to 35 days • Progesterone levels greater than 13 nmol/L in the luteal phase • Normal circulating serum levels of free testosterone, DHEAS, androstenedione, and 17-hydroxyprogesterone serum levels • No discontinuation of the therapy **Exclusion criteria of the trial**

	• Patients with abnormal results on routine laboratory tests (haematologic examination, fasting plasma glucose, serum creatinine, liver function, serum electrolytes, and lipid analysis) • Abnormal hormonal screening variables (serum cortisol, free T4, thyroid-stimulating hormone, FSH, LH, and prolactin) Randomised N = 41 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: CPA group 20.9 (1.3), finasteride group 21.8 (1.7), spironolactone group 21.1 (1.3) F-G score: CPA group 11.17 (1.27), finasteride group 12.08 (1.08), spironolactone group 11.21 (1.22) Free T (pmol/L): CPA group 20.61 (3.42), finasteride group 18.80 (2.34), spironolactone group 20.30 (3.11) Androstenedione (nmol/L): CPA group 4.21 (1.87), finasteride group 4.54 (2.43), spironolactone group 5.98 (2.37) DHEAS (µmol/L): CPA group 5.12 (2.09), finasteride group 4.32 (1.26), spironolactone group 4.68 (1.76)
Interventions	**Intervention** • Cyproterone acetate, 12.5 mg/day for the first 10 days of the cycle for 12 months (13) **Comparator 1** • Finasteride, 5 mg/day for 12 months (13) **Comparator 2** • Spironolactone, 100 mg/day for 12 months (15) Patients were requested not to use cosmetic treatments, such as shaving, depilatory, hot wax, or hair removal by electrolysis. All patients received oral contraceptives for at least 2 years
Outcomes	Assessments (4): baseline, month 6, 12, and 24 **Outcomes of the trial** (as reported) 1. Serum DHEAS, free testosterone, androstenedione, and 17-hydroxyprogesterone * 2. Ferriman-Gallwey score * 3. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Lumachi 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote (page 943): "The choice of treatment for each patient was made by using a random number table." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Luque-Ramírez 2007

Methods	Randomised, open-label, active-controlled study Setting Departments of Endocrinology and Biochemistry-Research, Hospital Universitario Ramón y Cajal and Universidad de Alcala, Madrid, Spain Date of study April 2004 to December 2006. Duration of intervention 24 weeks
Participants	N = 34 Mean age = 24 years **Inclusion criteria of the trial**

	• PCOS, diagnosis based on the presence of clinical and/or biochemical hyperandrogenism, oligo-ovulation, and exclusion of secondary aetiologies • Hirsutism was defined by a modified Ferriman-Gallwey score > 7 • Oligomenorrhoea (more than 6 cycles longer than 36 days in the previous year) or amenorrhoea (absence of menstruation for 3 consecutive months), or luteal phase progesterone measurements less than 4 ng/ml (12.72 nmol/L) in women with regular menstrual cycles were considered indicative of oligo-ovulation **Exclusion criteria of the trial** • Secondary aetiologies, including hyperprolactinaemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, and virilising tumours • Hypertension • Diabetes mellitus • Cardiovascular events • Treatment with oral contraceptives, antiandrogens, insulin sensitisers, or drugs that might interfere with blood pressure regulation, lipid profile, or carbohydrate metabolism, < 6 months prior to study entry Randomised N = 34 Withdrawals/losses to follow-up • 7/34 (21%); 0/15 in EE/CPA group and 7/19 in metformin group • Protocol violation; 0/15 in EE/CPA group and 3/19 in metformin group • Gastrointestinal side effects; 0/15 in EE/CPA group and 2/19 in metformin group • Pregnancy; 0/15 in EE/CPA group and 1/19 in metformin group • Lost to follow-up; 0/15 in EE/CPA group and 1/19 in metformin group Baseline data (mean (SD)) BMI: EE/CPA group 29.2 (5.7), metformin group 30.5 (6.9) Waist/hip ratio: EE/CPA group 0.79 (0.06), metformin group 0.82 (0.11) F-G score: EE/CPA group 11 (5), metformin group 10 (6) Free testosterone (ng/dl): EE/CPA group 1.1 (0.4), metformin group 1.3 (0.6) Androstenedione (ng/ml): EE/CPA group 3.5 (0.8), metformin group 3.9 (1.1) DHEAS (ng/dl): EE/CPA group 2738 (1022), metformin group 2250 (933)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 24 weeks (15) **Comparator** • Metformin 850 mg b.i.d. for 24 weeks (19)
Outcomes	Assessments (3): baseline, week 12, and 24 **Outcomes of the trial** (as reported) 1. Clinical and anthropometrical variables (Ferriman-Gallwey score, BMI, waist circumference, and waist to-hip ratio) * 2. Percentage of body fat with respect to total body weight was estimated using a body fat monitor 3. Serum free testosterone, androstenedione, and DHEAS * 4. Glucose, insulin, oral glucose tolerance test 5. Circulating HDL cholesterol, phospholipid levels, total cholesterol, triglycerides, LDL cholesterol, apolipoprotein, lipoprotein

	* Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2453): "...were randomized. .." and "Simple randomization was conducted using blocks of 10 sealed opaque envelopes assigning five patients to receive Diane 35 Diario and five patients to receive metformin." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 2453): "...10 sealed opaque envelopes assigning five patients to receive. .." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 2453): "No masking method was used after randomization." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 2453): "No masking method was used after randomization." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	7/34 (21%); 0/15 in EE/CPA group and 7/19 in metformin group, reasons reported. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Other bias	Low risk	Quote (page 2460): "This study was supported by the Spanish Ministry of Health and Consumer Affairs, Instituto de Investigación Carlos III Grants Fondo de Investigacio´ n Sanitaria PI050341 and PI050551 and Red de Diabetes y Enfermedades Metabólicas Asociadas (REDIMET) RD06/0015/0007; Ministry of Education and Science Grant SAF2005-07038; and by economic aid from Hospital Ramón y Cajal." Comment: we judged this as at a low risk of bias

Maciel 2004

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Gynecology of Federal University of São Paulo, São Paulo, Brazil Date of study October 1997 until December 1999. Duration of intervention 6 months
Participants	N = 34 Mean age = 21 years **Inclusion criteria of the trial** • PCOS • Women must have history of (1) chronic anovulation since the menarche, as evidenced by either amenorrhoea or oligomenorrhoea (less than 6 menstrual periods in the last year); (2) clinical or laboratory evidence of hyperandrogenism (determined by serum hormonal concentration, and Ferriman and Gallwey score); (3) no secondary causes of anovulation; (4) and no present use of lipid-lowering drugs, antidiabetic medications, or hormonal contraception (in the last 3 months) **Exclusion criteria of the trial** • Cushing's syndrome • Late-onset 21-hydroxylase deficiency • Thyroid dysfunction • Hyperprolactinaemia • Androgen-secreting tumours • Diabetes mellitus • Evidence of chronic renal or hepatic disease Randomised N = 34 Withdrawals/losses to follow-up • 5/34 (15%); 2/17 in metformin group, 3/17 in placebo group • Pregnancy; 1/17 in metformin group, 1/17 in placebo group • Unknown reason; 0/17 in metformin group, 2/17 in placebo group • Diarrhoea; 1/17 in metformin group, 0/17 in placebo group Baseline data (mean (SEM))

	BMI: non obese placebo group 25.1 (1.6), obese placebo group 35.8 (1.5) non obese metformin group 25.3 (2.1), obese metformin group 37.2 (1.7) F-G score: non obese placebo group 8.5 (2.1), obese placebo group 8.9 (2.4), non obese metformin group 8.2 (1.2), obese metformin group 8.5 (2.9)
Interventions	**Intervention** • Metformin 500 mg 3 times a day (17) **Comparator** • Placebo 3 times a day (17)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Prolactin, growth hormone, cortisol, TSH, triiodothyronine, and serum and free thyroxine, 17-hydroxyprogesterone, leptin 2. FSH, LH, total testosterone, DHEA, DHEAS, SHBG and androstenedione * 3. Glucose, total cholesterol and lipoproteins levels 4. BMI * 5. Ferriman-Gallwey score * 6. Post-treatment changes in frequency of cycles * 7. Transvaginal sonography of uterus and ovaries 8. Oral glucose tolerance test * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 356): "...two different treatment arms in a sequence determined by a computerized random-number generator" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 356): "All patients received a sealed envelope that contained either the number 1 or 2, corresponding to placebo or metformin 1.5 g/day, respectively" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 356): "During the study, patients and investigators were not aware of the treatment assignments. To avoid compromising the double-blinded design, an independent gynecologist recorded the oc-

		currence of side effects or physical changes such as menstrual bleeding“ and ”Study drugs were packaged in 30-day flasks (90 capsules). The patients were instructed to take one capsule every 8 hours during the study. A gynecologist who did not participate in the screening process or the distribution of the drugs performed the follow-up evaluations.“ Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by participants and investigators. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/34 (15%); 2/15 in metformin group, 3/14 in placebo group Comment: moderate and balanced number of drop-outs at follow-up, combined with the per-protocol analysis considered to be at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Mastorakos 2002

Methods	Randomised, active-controlled trial Setting Out-patient gynaecology clinic, University of Athens, Aretaieion Hospital, Athens, Greece Date of study Not reported. Duration of the intervention 12 months
Participants	N = 28 Mean age = 18 years **Inclusion criteria of the trial** • Adolescent girls (age range: 14 to 19 years) with clinically evoked and biologically confirmed hyperandrogenism and ≤ 6 menses during the past 12 months indicating chronic anovulation • The diagnosis of PCOS in these patients was based on the criteria established at the 1990 PCOS conference organised at the National Institutes of Health (Bethesda, Maryland) by National Institute of Child Health and Development (Dunaif 1992) **Exclusion criteria of the trial** • Nonclassic adrenal 21-hydroxylase deficiency • Hyperprolactinaemia • Androgen-secreting neoplasms • Hormonal medication, including combined oral contraceptives, for at least 6 months before the study Randomised N = 28 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: desogestrel/EE group 25.5 (1.79), CPA/EE group 24.84 (1.09) F-G score: desogestrel/EE group 15.71 (1.63), CPA/EE group 16.78 (1.15) Waist/hip ratio: desogestrel/EE group 0.77 (0.02), CPA/EE group 0.75 (0.01) Testosterone (ng/ml): desogestrel/EE group 1.04 (0.08), CPA/EE group 0.99 (0.10) Free testosterone (pg/ml): desogestrel/EE group 3.24 (0.24), CPA/EE group 3.20 (0.27) Androstenedione (ng/ml): desogestrel/EE group 3.77 (0.26), CPA/EE group 3.67 (0.27) DHEAS (ng/ml): desogestrel/EE group 2633.71 (352.38), CPA/EE group 2434.33 (229.13) SHBG (nmol/L): desogestrel/EE group 55.86 (9.63), CPA/EE group 59.07 (8.05)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 12 months (14) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 12 months (14)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score 2. Total cholesterol and triglycerides, HDL cholesterol and LDL cholesterol, apolipoproteins A-I, A-II, and B 3. Testosterone, free testosterone, SHBG, androstenedione, DHEAS

	* * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 921): "...patients were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "... computer generated" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "The randomization is performed by our computer technician who generates the random numbers and he is the only one to know in each study the allocation sequence until the moment of assignment." Comment: response provides insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias

Mastorakos 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Mastorakos 2006

Methods	Randomised, active-controlled trial Setting Out-patient gynaecology clinic, University of Athens, Aretaieion Hospital, Athens, Greece Date of study Not reported. Duration of the intervention 12 months
Participants	N = 36 Mean age = 17 years **Inclusion criteria of the trial** • Adolescent girls (age range: 14 to 19 years) with clinically evoked and biologically confirmed hyperandrogenism and ≤ 6 menses during the past 12 months indicating chronic anovulation • The diagnosis of PCOS in these patients was based on the criteria established at the 1990 PCOS conference organised at the National Institutes of Health (Bethesda, Maryland) by the National Institute of Child Health and Development (Dunaif 1992) **Exclusion criteria of the trial** • Adenoma-associated hyperprolactinaemia • Functional thyroidopathy • 21-hydroxylase deficiency associated with non-classic congenital adrenal hyperplasia • Androgen-secreting neoplasms • Diabetes mellitus Randomised N = 36 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SEM)) BMI: desogestrel/EE 25.8 (1.81), CPA/EE 25.4 (1.49) F-G score: desogestrel/EE 16.52 (1.74), CPA/EE 16.88 (1.27) Waist/hip ratio: desogestrel/EE 0.74 (0.07), CPA/EE 0.73 (0.06) Testosterone (ng/ml): desogestrel/EE 1.13 (0.09), CPA/EE 1.06 (0.10) Free testosterone (pg/ml): desogestrel/EE 3.27 (1.8), CPA/EE 3.24 (0.75) Androstenedione (ng/ml): desogestrel/EE 3.97 (0.35), CPA/EE 3.81 (0.29) DHEAS (ng/ml): desogestrel/EE 2694.13 (341.45), CPA/EE 2563.42 (357.65) SHBG (nmol/L): desogestrel/EE 35.31 (8.14), CPA/EE 29.18 (9.24)

Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 12 months (18) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 12 months (18)
Outcomes	Assessments (2): baseline and month 12 **Outcomes of the trial** (as reported) 1. Testosterone, free testosterone, 4-androstenedione, DHEAS), 17OH progesterone, SHBG, total cholesterol, LDL and HDL cholesterol subfractions, triglycerides, apolipoproteins (A-I, A-II, B), and lipoprotein * 2. Fasting glucose and insulin serum levels were measured and an oral glucose tolerance test 3. Abdominal ultrasound with a 5 mHz transducer was performed to assess the morphology and the volume of the uterus and ovaries 4. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review
Notes	Androgens, Ferriman-Gallwey score and abdominal ultrasound were assessed at baseline, but not after 12 months as stated in the protocol. None of our outcomes are addressed. After e-mail communication investigator provided Ferriman-Gallwey scores and androgen levels after 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 421): "Randomization was based on computer-generated random numbers" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "The randomization is performed by our computer technician who generates the random numbers and he is the only one to know in each study the allocation sequence until the moment of assignment" Comment: response provides insufficient information to permit a clear judgement

Mastorakos 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

McLellan 1989

Methods	Randomised, placebo-controlled trial Setting University Departments of Medicine and Dermatology, Western Infirmary, Glasgow, UK Date of study Not reported. Duration of the intervention 9 months
Participants	N = 38 Mean age = not reported **Inclusion criteria of the trial** • Women with presumptive diagnosis of idiopathic hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 38 Withdrawals/losses to follow-up • 16/38 (42%); 8 pairs • Non-compliance; 2 pairs (n = 4) • Menorrhagia in active treatment group; 3 pairs (n = 6) • Personal reasons unrelated to drug therapy; 3 pairs (n = 6) Baseline data (mean (SEM)) Testosterone (nmol/L): spironolactone group 3.3 (0.3), placebo group 3.1 (0.2) Androstenedione (nmol/L): spironolactone group 8.2 (1.0), placebo group 9.1 (1.0)

	DHEAS (μmol/L): spironolactone group 7.0 (0.8), placebo group 6.6 (1.0) SHBG (nmol/L): spironolactone group 30.2 (4.9), placebo group 30.4 (3.7)
Interventions	**Intervention** • Spironolactone 100 mg/day for 9 months **Comparator** • Placebo for 9 months
Outcomes	Assessments (5): baseline, week 6, 12, 24, and 36 **Outcomes of the trial** (as reported) 1. Change in hair diameter * 2. Subjective effect of treatment; 5-point Likert scale * 3. Subjective effect on acne, greasiness of the skin and hair * 4. Serum androgens, gonadotrophins, prolactin, canrenone * *Denotes outcomes prespecified for this review
Notes	The patients were paired, one member of each pair being randomised to active treatment and the other to placebo. > 40% losses to follow-up. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 459): "The patients were paired, one member of each pair being randomized to active treatment and the other to placebo. Pairs were matched primarily for menstrual regularity (or irregularity) but also, as closely as possible, for duration and degree or hirsutism (Ferriman & Gallwey Index), family history of hirsutism, age of menarche and presence of acne to ensure equal allocation to the treatment groups of any patients with unrecognized polycystic ovary syndrome." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment,

		was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 459): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 19): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	16/38 (42%); 8 pairs, per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 462): "The study was supported by a grant from G.D. Searle & Co. Ltd." Comment: G.D. Searle & Co. Ltd is the manufacturer of spironolactone. A potential risk of bias cannot be excluded

Meyer 2007

Methods	Randomised, open-label, active-controlled trial Setting Monash University Vascular Medicine Department at Dandenong Hospital, Melbourne, Victoria, Australia Date of study 2003 until 2005. Duration of the intervention 6 months
Participants	N = 110 Mean age = 31 years **Inclusion criteria of the trial** • Overweight women (BMI > 27 kg/m^2) with PCOS • PCOS diagnosis was based on perimenarchal onset of irregular cycles (21 days or 35 days) and clinical manifestations of hyperandrogenism (hirsutism or acne) or biochemical hyperandrogenism with elevation of at least one circulating ovarian androgen (according to 1990 National Institutes of Health criteria (Teede 2006)) **Exclusion criteria of the trial** • Secondary causes of amenorrhoea and hyperandrogenism (clinical screening and early follicular 17-hydroxyprogesterone levels) • Diabetes • Pregnant women • Medications affecting insulin resistance, including all OCPs < 3 months prior to treatment Randomised N = 110 Withdrawals/losses to follow-up • 10/110 (9%); 1/37 in metformin group, 4/35 in high dose OCP, 5/38 in low dose OCP • 8/10 for personal reasons, 1 from each OCP group for mood swings Baseline data (mean) BMI: metformin group 36.3, high-dose OCP 36.5, low-dose OCP 35.5 Waist/hip ratio: metformin group 0.87, high-dose OCP 0.84, low-dose OCP 0.86 F-G score: metformin group 8.80, high-dose OCP 6.7, low-dose OCP 6.4 Testosterone (nmol/L): metformin group 2.50, high-dose OCP 2.10, low-dose OCP 2.76 DHEAS (µmol/L): metformin group 5.49, high-dose OCP 4.89, low-dose OCP 4.29 SHBG (nmol/L): metformin group 30.1, high-dose OCP 33.9, low-dose OCP 33.5
Interventions	**Intervention** • Metformin 1 g b.i.d. for 6 months (37) **Comparator 1** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (35) **Comparator 2** • OCP (ethinyl estradiol 30 µg + levonorgestrel 0.1 mg) + spironolactone 50 mg/day for 6 months (38) At screening, standard diet and lifestyle advice was delivered according to National Heart Foundation of Australia recommendations (www.heartfoundation.com.au)
Outcomes	Assessments (2): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Waist/hip ratio, BMI, Ferriman-Gallwey score, menstrual diaries

	* 2. Insulin resistance 3. Surrogate markers of cardiovascular disease (non-invasive arterial parameters, arterial stiffness, endothelial function) 4. DHEAS, SHBG, testosterone * 5. Cholesterol, HDL cholesterol, LDL cholesterol, triglycerides * Denotes outcomes prespecified for this review
Notes	Unclear how many women with PCOS were hirsute, the mean hirsutism score was only > 8 in the metformin group. See Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 472): "At randomization, 110 subjects were allocated to one of three groups based on computer-generated random numbers" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 472): "...open-label..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 472): "...open-label..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/110 (9%); 1/37 in metformin group, 4/35 in high-dose OCP, 5/38 in low-dose OCP. Per-protocol analysis Comment: low and balanced number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 477): "This work was an investigator- initiated trial funded by a competitive CVL grant sponsored by Pfizer Australia and through internal department funds. Pfizer Australia provided the aldactone, and Douglas Pharmaceuticals Australia provided the metformin." Comment: a potential risk of bias cannot be excluded

Moghetti 2000

Methods	Randomised, double-blind, placebo-controlled trial Setting Division of Endocrinology and Metabolic Diseases, University of Verona, and Division of Dermatology, University of Bologna, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 40 Mean age = 20 years **Inclusion criteria of the trial** • Moderate to severe hirsutism **Exclusion criteria of the trial** • Cushing's syndrome • Adrenal enzyme defects • Adrenal and ovarian tumours • Hyperprolactinaemia • Thyroid dysfunction • Other disease • OCP or antiandrogen drugs < 12 months prior to study entry Randomised N = 40 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SEM)) BMI: spironolactone group 25.3 (1.4), flutamide group 23.6 (1.0), finasteride group 23.3 (0.7), placebo group 25.8 (2.0) Modified F-G score: spironolactone group 16.9 (0.9), flutamide group 17.5 (1.5), finasteride group 18.4 (1.3), placebo group 17.2 (1.6) Menses (irregular/regular): spironolactone group 2/8, flutamide group 8/2, finasteride

Moghetti 2000 (*Continued*)

	group 4/6, placebo group 4/6 PCOS/other: spironolactone group 4/6, flutamide group 8/2, finasteride group 4/6, placebo group 5/5
Interventions	**Intervention** • Spironolactone 100 mg/day for 6 months (10) **Comparator 1** • Flutamide 250 mg/day for 6 months (10) **Comparator 2** • Finasteride 5 mg/day for 6 months (10) **Comparator 3** • Placebo for 6 months (10) Sexually active women were advised to use barrier contraceptive methods or intrauterine devices
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Diameter of hair (5 plucked hairs from linea alba) * 3. Participant's subjective opinion; 4-point Likert scale * 4. Questionnaire specifying cosmetic measure for hair removal 5. Serum gonadotropins, total testosterone, free testosterone, DHEAS, androstenedione, 3α-androstanediol glucuronide * 6. C_{19} and C_{21} steroid metabolites in 24-hour urine 7. Adverse events * * Denotes outcomes prespecified for this review
Notes	The Negri 2000 study (additional reference to this study) reports different outcomes, not relevant to our systematic review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 90): "...randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "...were computer-generated." Comment: probably done

Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: central allocation via the pharmacy Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 90): "...double-blind treatments, once daily orally as a wafer capsule. .." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators and participants. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	Although serum total testosterone and androstenedione were prespecified endocrine assessments, no corresponding data were reported Comment: we judged this as at a high risk of bias After e-mail communication: these data were provided by the PI and the judgement has been amended to low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Moghetti 2000B

Methods	Randomised, double-blind, placebo-controlled trial Setting Division of Endocrinology and Metabolic Diseases, University of Verona, Verona, Italy Date of study Not reported. Duration of intervention 26 weeks
Participants	N = 23 Mean age = 23 years **Inclusion criteria of the trial** • PCOS • 18 to 35 years • Diagnosis of PCOS was based on the presence of hyperandrogenic chronic anovulation, after exclusion of Cushing's syndrome, late-onset 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinaemia, or androgen-secreting tumours, according to recommendations of the NIH consensus development conference on PCOS (Dunaif 1992) **Exclusion criteria of the trial** • Other diseases or taking medications Randomised N = 23 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: metformin group 27.1 (1.5), placebo group 32.6 (1.1) Waist/hip ratio: metformin group 0.84 (0.02), placebo group 0.86 (0.02) Free testosterone (pmol/L): metformin group 11.6 (1.8), placebo group 10.7 (1.4) Androstenedione (nmol/L): metformin group 12.5 (1.5), placebo group 10.3 (0.7) DHEAS (µmol/L): metformin group 6.6 (0.7), placebo group 5.2 (0.5) SHBG (nmol/L): metformin group 35.6 (8.2), placebo group 33.5 (5.7)
Interventions	**Intervention** • Metformin 500 mg once daily to 3 times a day for 26 weeks (12) **Comparator** • Placebo for 26 weeks (11)
Outcomes	Assessments (2): baseline and week 26 **Outcomes of the trial** (as reported) 1. Assessment of menstrual history, with recording of menses in the 6-month periods before the study and during treatment * 2. Physical examination for body weight, waist/hip ratio, hirsutism score, and blood pressure * 3. Serum gonadotropins, androgens (total and free testosterone, DHEAS, androstenedione), 17-hydroxyprogesterone, estradiol, SHBG and lipoproteins (total and HDL cholesterol, triglycerides) * 4. GnRH-agonist challenge with measurement of serum 17-hydroxyprogesterone, gonadotropins and estradiol, 24 hours after 0.1 mg buserelin subcutaneously

	5. Oral glucose tolerance test, with plasma glucose and insulin measurements on samples obtained every 30 minutes for 2 hours 6. Insulin sensitivity assessment by the glucose clamp technique 7. Adverse events * *Denotes outcomes prespecified for this review
Notes	Quote (page 140): "Eighteen out of the 23 women included in protocol A received metformin in an open design providing treatment for an unscheduled duration after the completion of the double-blind study" Quote (page 141): "Subjects with hirsutism were equally distributed in the two groups, and no significant change in hirsutism score was found after treatment in either group (data not shown)." After e-mail communication, we received additional information, see Table 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 140): "Women were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "...were computer-generated." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: central allocation via the pharmacy Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 140): "...assigned to double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Moghetti 2000B (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 140): "...assigned to double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 139): "This work was supported by grants from the Italian Ministry of Higher Education and Scientific Research, and the Regione del Veneto (DGRV 964, n.652 and n.693)." There is baseline imbalance regarding BMI, but the number of subjects with hirsutism were equally distributed Comment: we judged this as at a low risk of bias

Moltz 1984

Methods	Randomised, double-blind, placebo-controlled trial Setting Multi-centre (9) in Germany Date of study Not reported. Duration of intervention 9 to 12 months
Participants	N = 164 Mean age = not reported **Inclusion criteria of the trial** • Women with moderate to severe seborrhoea, acne, and hirsutism **Exclusion criteria of the trial** • Androgen-producing tumours Randomised N = 164 Withdrawals/losses to follow-up

	• Unclear; 29/82 (35%) dropped out in OCP + CPA group after 9 months and 41/82 (50%) after 12 months. Unclear how many dropped out in the control group Baseline data Only reported for the first 15 participants in each group
Interventions	**Intervention** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) + 10 mg cyproterone acetate first 15 days of pill cycle for 9 to 12 months (82) **Comparator** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) for 9 to 12 months (82)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Improvement of seborrhoea * 2. Improvement of hirsutism on face, legs, and belly * 3. Improvement of acne * * Denotes outcomes prespecified for this review
Notes	Unclear how many dropped out in control group, unclear how many were hirsute in control group. Mainly data are reported on the OCP + CPA group, and hardly any data on control group. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 48): "...erhielten nach zufälliger Verteilung..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 48): "...einer Doppelblind-Studie..." The control group received placebo tablets instead of the 10 mg CPA during the first 15 days of pill cycle

		Comment: the report did not provide sufficient detail about the specific measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	29/82 (35%) dropped out in OCP + CPA group after 9 months and 41/82 (50%) after 12 months. Unclear how many dropped out in the control group Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Insufficient information to permit a clear judgement

Morin-Papunen 2000

Methods	Randomised, active-controlled trial Setting Reproductive Endocrine Unit at Oulu, University Hospital, Oulu, Finland Date of study Not reported. Duration of intervention 6 months
Participants	N = 32 Mean age = 30 years **Inclusion criteria of the trial** • Obese (BMI > 27 kg/m^2) women with PCOS • Criteria for PCOS were as defined by Homburg 1996 **Exclusion criteria of the trial** • Diabetic subjects • Smokers and alcohol users • Sex hormones or drugs known to affect lipid metabolism < 2 months prior to

	study entry Randomised N = 32 Withdrawals/losses to follow-up • 14/32 (44%); 6/14 in metformin group, 8/16 in EE + CPA group • Moved 1/32; 1/14 in metformin group • Personal reasons 2/32; 1/14 in metformin group, 1/16 in EE + CPA group • Manifest diabetes mellitus 3/32; 2/14 in metformin group, 1/16 in EE+ CPA group • Adverse events 3/32; 2/14 in metformin group, 1/16 in EE+ CPA group • No reason reported 5/32; 5/16 in EE + CPA group Baseline data (mean (SEM)) BMI: metformin group 32.5 (1.1), EE + CPA group 37.2 (1.8) Waist/hip ratio: metformin group 0.89 (0.04), EE + CPA group 0.86 (0.01) F-G score: metformin group 10.3 (1.9), EE + CPA group 9.0 (2.1)
Interventions	**Intervention** • Metformin 500 to 1000 mg b.i.d. for 6 months (14) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (16)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Transvaginal ultrasonography 2. Waist and hip circumferences, BMI * 3. OGTT 4. Ferriman-Gallwey score * 5. Assessment of insulin sensitivity; the euglycaemic hyperinsulinaemic clamp technique 6. Calorimetry 7. SHBG, LH, FSH, androstenedione, DHEA, DHEAS, 17-hydroxyprogesterone, testosterone, free testosterone * * Denotes outcomes prespecified for this review
Notes	Unclear how many were randomised to each group; unclear to which group the 6/14 women that dropped out for unreported reasons were allocated. High number of total losses (44%), see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 3162): "...were randomized to either..." Comment: insufficient detail was reported about the method used to generate the allo-

		cation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail contact, quote: "...it was performed by the hospital pharmacy with 1: 1 allocation in random blocks of ten using two computer-generated lists." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail contact, quote: "the allocation was concealed in a closed envelope where the number of the patient was written. The participant knew the allocation after she had accepted to participate." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	14/32 (44%); unclear how many in each group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Morin-Papunen 2000 (*Continued*)

Other bias	Low risk	Quote (page 3161): "Supported by grants from the Sigrid Jusenius Foundation, the Academy of Finland, and the Finnish Association of Obstetrics and Gynecology." Comment: we judged this as at a low risk of bias

Morin-Papunen 2003

Methods	Randomised, active-controlled trial Setting Reproductive Endocrine Unit at Oulu, University Hospital, Oulu, Finland Date of study Not reported. Duration of intervention 6 months
Participants	N = 17 Mean age = 28 years **Inclusion criteria of the trial** • Non-obese (BMI < 25 kg/m^2) women with PCOS • Criteria for PCOS were as defined by Homburg 1996 **Exclusion criteria of the trial** • Diabetic subjects • Smokers and alcohol users • Sex hormones or drugs known to affect lipid metabolism < 2 months prior to study entry Randomised N = 17 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SEM)) BMI: metformin group 22.5 (0.8), EE + CPA group 21.8 (0.8) Waist/hip ratio: metformin group 0.78 (0.01), EE + CPA group 0.79 (0.02) F-G score: metformin group 7.88 (1.9), EE + CPA group 5.2 (0.6)
Interventions	**Intervention** • Metformin 500 to 1000 mg b.i.d. for 6 months (8) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (9)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Transvaginal ultrasonography, blood pressure 2. Waist and hip circumferences, BMI * 3. OGTT 4. Ferriman-Gallwey score * 5. Assessment of insulin sensitivity; the euglycaemic hyperinsulinaemic clamp

	technique 6. Calorimetry 7. SHBG, LH, FSH, androstenedione, DHEA, DHEAS, 17-hydroxyprogesterone, testosterone, free testosterone * *Denotes outcomes prespecified for this review
Notes	No separate data on women that were hirsute, means of Ferriman-Gallwey score in both groups were below threshold for hirsutism (Ferriman-Gallwey score > 8), see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 149): "...were randomized to either..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail contact, quote: "...it was performed by the hospital pharmacy with 1:1 allocation in random blocks of ten using two computer-generated lists." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail contact, quote: "...the allocation was concealed in a closed envelope where the number of the patient was written. The participant knew the allocation after she had accepted to participate." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Morin-Papunen 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 154): "Supported by grants provided by the University of Oulu, the Finnish Association of Obstetrics and Gynecology, the Sigrid Jusenius Foundation, and the Academy of Finland." Comment: we judged this as at a low risk of bias

Murdoch 1987

Methods	Randomised, double-blind, placebo-controlled trial Setting The University of Newcastle upon Tyne, Princess Mary Maternity Hospital, Newcastle upon Tyne, UK Date of study Not reported. Duration of study 1 year
Participants	N = 22 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute women with PCOS • PCOS based on the clinical symptoms oligomenorrhoea or amenorrhoea and hirsutism dating from the menarche. In all the subjects the hirsutism score was > 8 using the scoring system described by Ferriman and Gallwey. In addition the patients had elevated serum LH concentrations (> 6 u/L); the LH:FSH ratio was > 2:1 and plasma testosterone and androstenedione concentration were at or above the upper limits of the normal female range **Exclusion criteria of the trial** • Other endocrine abnormalities Randomised N = 22 Withdrawals/losses to follow-up

	• 6/22 (27%); 4/11 in bromocriptine group, 2/11 in placebo group • Social reasons; 1/11 in bromocriptine group, 1/11 in placebo group • Side effects; 3/11 in bromocriptine group, 1/11 in placebo group Baseline data (range) Testosterone (nmol/L): bromocriptine group from 3.0 to 6.8, placebo group 3.0 to 5.1 Androstenedione (nmol/L): bromocriptine group 9.5 to 39.2, placebo group 9.0 to 42.2
Interventions	**Intervention** • Bromocriptine 2.5 mg 3 times a day for 1 year (11) **Comparator** • Placebo for 1 year (11)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Subjective assessment of hirsutism; 3-point Likert scale * 2. Objective assessment; photographic evaluation of number of hairs and growth rate * 3. Menstruation frequency * 4. Androstenedione, testosterone, estradiol, estrone, SHBG * 5. LH and FSH * Denotes outcomes prespecified for this review
Notes	Individual participant data are provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 358): "...were allocated randomly..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement

Murdoch 1987 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 358): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 358): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	6/22 (27%); 4/11 in bromocriptine group, 2/11 in placebo group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Unclear risk	Quote (page 364): "We are grateful for the financial support for this study provided by Sandoz UK Ltd." Comment: a potential risk of bias cannot be excluded

Müderris 2000

Methods	Randomised, active-controlled trial Setting Departments of Gynecology and Obstetrics and Endocrinology at Erciyes University Medical Faculty, Kayseri, Turkey Date of study Not reported. Duration of intervention 12 months
Participants	N = 70 Mean age = 23 years **Inclusion criteria of the trial**

	• Hirsute women **Exclusion criteria of the trial** • Medication < 6 months prior to study entry Randomised N = 70 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) PCOS: flutamide group 16/35, finasteride group 21/35 F-G score: flutamide group 17.8 (5.8), finasteride group 19.1 (6.1) Testosterone (ng/dl): flutamide group 74.3 (24.9), finasteride group 65.7 (39.4) Free testosterone (pg/ml): flutamide group 3.6 (1.4), finasteride group 3.9 (2.0) Androstenedione (ng/ml): flutamide group 3.3 (0.9), finasteride group 3.1 (1.3) DHEAS (ng/ml): flutamide group 192.0 (59.5), finasteride group 299.8 (148.9) SHBG (nmol/L): flutamide group 28.9 (7.1), finasteride group 33.7 (14.9)
Interventions	**Intervention** • Flutamide 250 mg/day for 12 months (35) **Comparator** • Finasteride 5 mg/day for 12 months (35)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Total testosterone, free testosterone, FSH, LH, E2, DHEAS, androstenedione, 17a-hydroxyprogesterone and SHBG * 3. Haematologic, hepatic, renal function analysis 4. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 985): "Subjects were assigned randomly in a 1:1 ratio" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Müderris 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Navali 2012

Methods	Randomised, active-controlled trial Setting Al-Zahra Educational and Health Hospital Center and Sheikh Alra' is Clinic of Tabriz University of Medical Sciences, Tabriz, Iran Date of study Not reported. Duration of intervention 6 months
Participants	N = 100 Mean age = 28 years **Inclusion criteria of the trial** • Women with PCOS **Exclusion criteria of the trial** • Not reported Randomised N = 100

	Withdrawals/losses to follow-up • 6/100 (6%); 6/50 in pioglitazone group due to weight gain, these were replaced by new participants Baseline data (mean (SEM)/percentage) BMI: metformin group 27.9 (0.9), pioglitazone group 27.8 (0.7) Primary infertility: metformin group 44%, pioglitazone group 34% Secondary infertility: metformin group 30%, pioglitazone group 38% Hirsutism: metformin group 31/50, pioglitazone group 32/50
Interventions	**Intervention** • Metformin 500 mg 3 times a day for 6 months (50) **Comparator** • Pioglitazone 15 mg b.i.d. for 6 months (50)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Clinical and laboratory parameters including pattern of menstrual cycles, hirsutism, fasting blood sugar, hyperinsulinaemia, oral glucose tolerance test, glucose, insulin, free testosterone and prolactin * 2. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 358): "...were randomly divided..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Navali 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/100 (6%); 6/50 in pioglitazone group due to weight gain, these were replaced by new participants Comment: low number of losses to follow-up and although replaced, we judged this as at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	Although prespecified as outcomes, serum free testosterone and prolactin at end of study, were unreported Comment: we judged this as at unclear risk of bias
Other bias	Low risk	The study appears to be free of other sources of bias

O'Brien 1991

Methods	Randomised, active-controlled trial Setting Department of Endocrinology, Austin Hospital, Heidelberg, Victoria, Australia Date of study Not reported. Duration of intervention 6 months
Participants	N = 50 Mean age = 32 years **Inclusion criteria of the trial** • Hirsute women based on PCOS (8) or idiopathic hirsutism (42) **Exclusion criteria of the trial** • Cliteromegaly and severe virilisation Randomised N = 50 Withdrawals/losses to follow-up • 4/50 (8%); 1/27 in CPA group, 3/23 in spironolactone group • Personal reasons; 0/27 in CPA group, 2/23 in spironolactone group • Adverse events; 1/27 in CPA group, 1/23 in spironolactone group Baseline data (mean (SEM)) Total hair diameters (μm): spironolactone group 182 (9.2), CPA group 184 (12.6) Testosterone (nmol/L): spironolactone group 2.3 (0.2), CPA group 2.5 (0.2) DHEAS (μmol/L): spironolactone group 8.1 (0.8), CPA group 8.1 (0.7) Androstenedione (nmol/L): spironolactone group 6.0 (0.4), CPA group 6.1 (0.6) SHBG (nmol/L): spironolactone group 35.8 (5.0), CPA group 34.3 (3.9)

O'Brien 1991 (*Continued*)

Interventions	**Intervention** • Spironolactone 100 mg/day + triphasic OCP for 6 months (23) **Comparator** • Cyproterone acetate 100 mg/day + 30 µg ethinyl estradiol on days 5 to 14 of menstrual cycle for 6 months (27)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Testosterone, androstenedione, DHEAS, SHBG * 2. Electrolytes, urea, creatinine, liver function tests 3. Total hair shaft diameter, medullary diameter; 10 hairs plucked from facial area * 4. Record of frequency with which participants performed cosmetic measures 5. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1008): "Randomization was performed with subjects stratified for the presence of PCO." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blind-

O'Brien 1991 (*Continued*)

		ing
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/50 (8%); 1/27 in CPA group, 3/23 in spironolactone group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Onalan 2005

Methods	Randomised, double-blind, placebo-controlled trial Setting Reproductive Endocrinology Unit of Centrum Clinic, Ankara, Turkey Date of study Not reported. Duration of intervention 6 months
Participants	N = 139 Mean age = 27 years **Inclusion criteria of the trial** • Oligomenorrhoea or amenorrhoea as a surrogate for oligo-anovulation since menarche and who also had at least one of the criteria of hyperandrogenism including a hirsutism score of more than 7 (according to Ferriman and Gallwey) and/or an elevated serum concentrations of free testosterone (> 4 ng/dl) were diagnosed as PCOS, after excluding all other causes of hyperandrogenism **Exclusion criteria of the trial** • Medications known to alter insulin secretion or action • Endocrinopathies (including Cushing's syndrome, non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, hyperprolactinaemia or thyroid dysfunction, type 2 diabetes) Randomised N = 139 Withdrawals/losses to follow-up • 23/139 (17%); 17/72 in metformin group, 6/67 in placebo group • Gastrointestinal side effects; 15/72 in metformin group • Headache; 4/139 unclear which group • Unreported reason; 4/139 Baseline data See 'Notes'

Interventions	**Intervention** • Metformin 850 mg b.i.d. or 3 times a day according to BMI for 6 months (72) **Comparator** • Placebo for 6 months (67) Patients were instructed not to modify their usual eating habits throughout the study
Outcomes	**Outcomes of the trial** (as reported) 1. Serum FSH, LH, estradiol, progesterone, prolactin, testosterone, free testosterone, androstenedione, insulin, cortisol, TSH, DHEAS, SHBG * 2. Cholesterol, triglyceride, LDL, HDL 3. Ovulation * 4. Weight, height, waist-hip circumferences, BMI * 5. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review
Notes	Participants were randomised into 6 groups according to BMI and normo- or hyperinsulinaemic, of which half received metformin and remainder placebo, so total of 12 groups, listing baseline criteria for 12 groups is not feasible

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 205): "Patients were randomized on either metformin or placebo therapies according to the code provided by computer generated randomization in blocks of four" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 204): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear

Onalan 2005 (*Continued*)

		judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 204): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	23/139 (17%); 17/72 in metformin group, 6/67 in placebo group. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Oner 2011

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, Faculty of Medicine, Erciyes University, Kayseri, Turkey Date of study Not reported. Duration of intervention 6 months
Participants	N = 50 Mean age = 23 years **Inclusion criteria of the trial** • Nonpregnant, premenopausal women with moderate and severe hirsutism **Exclusion criteria of the trial** • Androgen-secreting adrenal or ovarian neoplasm (total plasma T < 200 ng/dl; plasma DHEAS) < 7000 ng/ml) • Cushing's syndrome • Congenital adrenal hyperplasia (early follicular phase plasma 17-hydroxyprogesterone < 3 ng/ml) or signs of virilisation • OCP or long acting progestogens < 12 months prior to study entry Randomised N = 50 Withdrawals/losses to follow-up

	• 3/50 (6%); 1/25 in EE 0.03 mg + DRSP group, 2/25 in EE 0.02 mg + DRSP group Baseline data (mean (SD)) BMI: EE 0.03 mg + DRSP group 23.4 (4.6), EE 0.02 mg + DRSP group 23.9 (6.6) Modified F-G score: EE 0.03 mg + DRSP group 17.3 (5.2), EE 0.02 mg + DRSP group 17.5 (4.8) Total testosterone (ng/dl): EE 0.03 mg + DRSP group 87.5 (43.7), EE 0.02 mg + DRSP group 80.5 (40.5) Free testosterone (pg/ml): EE 0.03 mg + DRSP group 2.9 (0.9), EE 0.02 mg + DRSP group 2.8 (0.7) Androstenedione (ng/ml): EE 0.03 mg + DRSP group 2.9 (0.3), EE 0.02 mg + DRSP group 3.0 (0.1) DHEAS (µg/ml): EE 0.03 mg + DRSP group 2.6 (1.3), EE 0.02 mg + DRSP group 2.6 (1.3) SHBG (nmol/L): EE 0.03 mg + DRSP group 45.3 (22.1), EE 0.02 mg + DRSP group 48.1 (30.2)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg 21 days of cycle) for 6 months (25) **Comparator** • OCP (ethinyl estradiol 20 µg + drospirenone 3 mg 24 days of cycle) for 6 months (25)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Total testosterone, free testosterone, androstenedione, DHEAS, SHBG, FSH, LH, estradiol * 3. Menstrual cycle, side effects * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 509): "...were randomized using a computer-generated randomization table" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been fore-

Oner 2011 (*Continued*)

		seen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 509): "To avoid interobserver errors, the same physician (I.I.M.) who was blinded to the treatments graded the degree of hirsutism according to a modified Ferriman-Gallwey (F-G) scoring system" Comment: although the assessment of this outcome was blinded, the other outcome assessments (by participants/healthcare providers) were not blinded Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/50 (6%); 1/25 in EE 0.03 mg + DRSP group, 2/25 in EE 0.02 mg + DRSP group. Per-protocol analysis Comment: low and balanced number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Oner 2011B

Methods	Randomised, active-controlled trial Setting Gynaecologic Endocrinology Clinic at Erciyes University, Kayseri, Turkey Date of study March 2008 until April 2009. Duration of intervention 24 weeks

Participants	N = 100 Mean age = 23 years **Inclusion criteria of the trial** • Women with PCOS with hirsutism and menstrual irregularity • PCOS according to Rotterdam Criteria PCOS 2004, i.e. the presence of at least 2 of the following 3 criteria: (1) oligo- or anovulation, (2) clinical and/or chemical signs of hyperandrogenism, and/or (3) polycystic ovaries; and exclusion of other aetiologies such as congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumours **Exclusion criteria of the trial** • Thyroid disease, hyperprolactinaemia, and diabetes mellitus • Drugs that could interfere with the normal function of the hypothalamic-pituitary-gonadal axis Randomised N = 100 Withdrawals/losses to follow-up • 25/100 (25%); 20/50 (40%) in metformin group, 5/50 (10%) in N-acetyl-cysteine group • Incomplete data or voluntary drop-out; 15/50 in metformin group, 5/50 in N-acetyl-cysteine group • Gastrointestinal side effects; 2/50 in metformin group, 0/50 in N-acetyl-cysteine group • Protocol violation; 2/50 in metformin group, 0/50 in N-acetyl-cysteine group • Lost to follow-up; 1/50 in metformin group, 0/50 in N-acetyl-cysteine group Baseline data (mean (SD)) BMI: metformin group 24.3 (6.2), N-acetyl-cysteine group 23.0 (4.6) F-G score: metformin group 11.4 (4.6), N-acetyl-cysteine group 12.2 (4.2) Total testosterone (ng/dl): metformin group 86.1 (48.4), N-acetyl-cysteine group 80.8 (41.1) Free testosterone (pg/ml): metformin group 2.06 (0.8), N-acetyl-cysteine group 2.7 (1.1) Androstenedione (ng/ml): metformin group 3.8 (1.6), N-acetyl-cysteine group 4.3 (1.3) DHEAS (ng/ml): metformin group 3090.7 (1711.4), N-acetyl-cysteine group 2608.8 (1121.4) SHBG (nmol/L): metformin group 43.7 (28.2), N-acetyl-cysteine group 47.5 (21.7)
Interventions	**Intervention** • Metformin 1500 mg/day for 6 months (50) **Comparator** • N-acetyl-cysteine 1800 mg/day for 6 months (50)
Outcomes	Assessments (3): baseline, week 12 and 24 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. BMI * 3. FSH, LH, DHEAS, 17-OH progesterone, total and free testosterone,

	androstenedione, TSH, prolactin * 4. Oral glucose tolerance test, glucose, insulin, HOMA * *Denotes outcomes prespecified for this review
Notes	Imbalance in losses to follow-up with 40% losses to follow-up in metformin arm and 10% in the N-acetyl-cysteine arm, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 128): "...were randomly divided into two groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	25/100 (25%); 20/50 (40%) in metformin group, 5/50 (10%) in N-acetyl-cysteine group. Per-protocol analysis Comment: the high and imbalanced drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section

Oner 2011B (*Continued*)

		appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Ortega-González 2005

Methods	Randomised, active-controlled trial Setting Department of Endocrinology, Instituto Nacional de Perinatología, México City, México Date of study Not reported. Duration of intervention 24 weeks
Participants	N = 57 Mean age = 29 years **Inclusion criteria of the trial** • Women with PCOS, aged 21 to 35 years, naive to any specific treatment, whose chief complaints were hirsutism (Ferriman-Gallwey score > 8) and/or sterility • The diagnosis of PCOS was based on at least 2 of the 3 following abnormalities: oligomenorrhoea or amenorrhoea, high serum androstenedione (> 2.9 ng/ml) and/or free testosterone (> 3.075 pg/ml) concentrations, and/or polycystic ovaries detected by ultrasound (Rotterdam Criteria PCOS 2004) • BMI > 25 kg/m^2, acanthosis nigricans, fasting hyperinsulinaemia (> 16 mIU/ml) and a fasting glucose/insulin (G/I) ratio < 4.5 **Exclusion criteria of the trial** • Type 2 diabetes mellitus • Hyperprolactinaemia • Thyroid disorders • Late-onset congenital adrenal hyperplasia • Cushing's syndrome Randomised N = 57 Withdrawals/losses to follow-up • 23/57 (40%); 10/27 in pioglitazone group, 13/30 in metformin group • Lost to follow-up; 5/27 in pioglitazone group, 5/30 in metformin group • Pregnancy; 5/27 in pioglitazone group, 3/30 in metformin group • Adverse events; 0/27 in pioglitazone group, 5/30 in metformin group Baseline data (mean (SEM)) BMI: pioglitazone group 32.3 (1.1), metformin group 34.4 (1.7) F-G score: pioglitazone group 15.4 (0.87), metformin group 16.4 (0.95)
Interventions	**Intervention** • Pioglitazone 30 mg/day for 24 weeks (27) **Comparator** • Metformin 850 mg 3 times a day for 24 weeks (30)

Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Height, weight, BMI, waist/hip ratio * 2. Ferriman-Gallwey score * 3. Oral glucose tolerance test, HOMA-IR, QUICKI, serum glucose, and insulin 4. Prolactin curve *Denotes outcomes prespecified for this review
Notes	Drop-outs in the metformin arm 43%, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 234): "...randomly allocated. ..Randomization was by random number tables" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 234): "The patients' number treatment codes were held and kept until the end of the trial by a third party (not participating in the study) and patients' names were disclosed after completion of the study." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	23/57 (40%); 10/27 in pioglitazone group, 13/30 in metformin group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias

Ortega-González 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 238): "Pharmaceutical companies had no role in the study design, data collection, data analysis, data interpretation or writing of the report. No funding of any kind was ever received to perform the study nor received by any of the participants in the study" and "We thank Eli Lilly Mexico, for the kind supply of pioglitazone tablets and to Laboratorios Pisa for the kind gift of metformin tablets." Comment: we judged this as at a low risk of bias

Otta 2010

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Endocrinology of Hospital Privado Centro Médico, de Córdoba, Córdoba, Argentina Date of study Not reported. Duration of intervention 4 months
Participants	N = 30 Mean age = 25 years **Inclusion criteria of the trial** • Women with PCOS, defined by hyperandrogenaemia (elevated serum testosterone concentrations) and oligomenorrhoea (cycles of 35 days or longer) or amenorrhoea (no menses in the last 6 months) after negative screening pregnancy test. Estimation of insulin resistance was derived from the HOMA index and other causes of hyperandrogenism (Cushing's syndrome, late-onset congenital adrenal hyperplasia, and androgen-secreting tumours) were excluded with appropriate diagnostic tests **Exclusion criteria of the trial** • Thyroid dysfunction • Hyperprolactinaemia • Diabetes • Severe infections • Cardiovascular, renal, or hepatic abnormalities • Any medications < 3 months prior to study entry Randomised N = 30 Withdrawals/losses to follow-up

	• 1/30 (3%); 1/15 in metformin group for lack of adherence to treatment, 0/15 in placebo group Baseline data (mean (SD)) F-G score: metformin group 11.73 (5.31), placebo group 13.5 (5.97) Acne: metformin group 8/15, placebo group 10/15 Androgenetic alopecia: metformin group 4/15, placebo group 5/15 BMI: metformin group 32.4 (6.7), placebo group 35.6 (4.98) Testosterone (ng/dl): metformin group 93.2 (22.01), placebo group 94.47 (18.22) Androstenedione (ng/ml): metformin group 2.87 (1.01), placebo group 2.98 (1.27)
Interventions	**Intervention** • Metformin from 500 mg once a day to 750 mg b.i.d. for 4 months (15) **Comparator** • Placebo for 4 months (15) Patients were also given a nutritional plan of 1500 calories daily. The women were advised to exercise (a minimum of 40 min of brisk walking per day, 4 times a week) and to use barrier contraceptives during the whole study
Outcomes	Assessments (5): baseline, month 1, 2, 3, and 4 **Outcomes of the trial** (as reported) 1. Menstrual cycles * 2. BMI, waist circumference, waist/hip ratio, blood pressure, acanthosis nigricans, and clinical signs of androgen excess (hirsutism measured by a modification of the Ferriman-Gallwey method, acne, seborrhoeic skin, and androgenetic alopecia) * 3. Total testosterone, androstenedione, DHEAS, progesterone, gonadotropins, insulin, glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides * 4. Oral glucose tolerance test 5. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 174): "The women were randomly assigned through a computerized allocation software..." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment,

		was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "Each pack of treatment was opaque and coded from the laboratory" Comment: form of central allocation, probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 174): "...in a double-blind way..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "Pills were exactly the same in shape and colour, and both (metformin and placebo) were tapered to one and a half pill BID" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 174): "...in a double-blind way..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: "Pills were exactly the same in shape and colour, and both (metformin and placebo) were tapered to one and a half pill BID." Comment: blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. We judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/30 (3%); 1/15 in metformin group for lack of adherence to treatment, 0/15 in placebo group. Per-protocol analysis Comment: low number of drop-outs at fol-

Otta 2010 (*Continued*)

		low-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote page 177: "This trial was done with a grant from National Institutes of Health (NCT00679679)." Comment: we judged this as at a low risk of bias

Paoletti 1999

Methods	Randomised, double-blind, placebo-controlled trial Setting Università degli Studi di Cagliari, Cagliari, and Università degli Studi di Modena, Modena, Italy Date of study Not reported. Duration of intervention for at least 5 months
Participants	N = 22 Mean age 23 years **Inclusion criteria of the trial** • Women with idiopathic hirsutism (IH) and non obese women with PCOS **Exclusion criteria of the trial** • Not reported Randomised N = 22 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean(SD)) Free testosterone (pg/ml): IH group 1.52 (0.63), PCOS group 2.51 (1.15), control group 1.32 (0.79) Total testosterone (ng/ml): IH group 0.62 (0.22), PCOS group 1.14 (0.32), control group 0.59 (0.52) DHEAS (ng/ml): IH group 1.80 (1.04), PCOS group 2.20 (0.37), control group 2.00 (1.92) Androstenedione (ng/ml): IH group 2.88 (0.66), PCOS group 5.03 (2.62), control group 2.22 (1.26)
Interventions	**Intervention** • Flutamide 250 mg b.i.d. for at least 5 months (12) **Comparator** • Placebo (10)

Outcomes	Assessments (2): baseline and month 4 **Outcomes of the trial** (as reported) 1. Fasting and oral glucose tolerance test stimulated levels of glucose, insulin and C-peptide 2. Liver function tests 3. Menstruation calendar * 4. Adverse events * 5. Hirsutism score (Ferriman-Gallwey score) * * Denotes outcomes prespecified for this review
Notes	The study also included 10 controls. There were no baseline values for hirsutism per treatment arm, only baseline values for women with idiopathic hirsutism and for women with PCOS, and as adverse events appear not to be reported, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 449): "...on the basis of a randomized, computer-generated list..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 449): "...in a double-blind fashion, oral treatment with flutamide (250 mg twice a day) or placebo (2 tablets of inert compound, visually indistinguishable from tablets of the active compound)." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator-assessed as well as participant-assessed (menstruation) Blinding of participants and key study personnel was ensured, and it is unlikely that

		the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	Adverse events, although a prespecified outcome, were not addressed Comment: we judged this as at unclear risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Pasquali 1986

Methods	Randomised, active-controlled trial Setting First Institute of Internal Medicine and the Institute of Physiopathology of Reproduction, University of Bologna, Bologna, Italy Date of study Not reported. Duration of intervention 3 months
Participants	N = 14 Mean age = 22 years **Inclusion criteria of the trial** • Women with PCOS and obesity (BMI > 28 kg/m^2) • PCOS was based on oligomenorrhoea or amenorrhoea, hirsutism, hyperandrogenism, elevated LH/FSH ratio, ultrasound of the ovaries **Exclusion criteria of the trial** • Not reported Randomised N = 14 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SEM)) BMI: hypocaloric diet + CPA/EE group 33.5 (1.5), hypocaloric diet alone group 32.0 (1.1)
Interventions	**Intervention** • Hypocaloric diet (1000 to 1200 kcal/day) + cyproterone acetate 50 mg/day (10 days) + ethinyl estradiol 50 µg (21 days) for 3 months (7) **Comparator** • Hypocaloric diet (1000 to 1200 kcal/day) for 3 months (7)

Outcomes	Assessments (4): baseline, month 1, 2, and 3 **Outcomes of the trial** (as reported) 1. Clinical condition, weight loss, adherence to diet * 2. Hormonal and biochemical evaluations, oral glucose tolerance test * 3. Glucose and insulin levels * Denotes outcomes prespecified for this review
Notes	Unclear how many women were hirsute, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 141): "The choice of treatment for each patient was randomized" Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported

Pasquali 1986 (*Continued*)

		Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 139): "This work was supported in part by a grant from the Ministry of Education, funds 40%, 1984." Comment: we judged this as at a low risk of bias

Pasquali 2000

Methods	Randomised, double-blind, active-controlled trial Setting Endocrine Unit of the Department of Internal Medicine and Gastroenterology of the S. Orsola-Malpighi Hospital of Bologna, Bologna, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 40 Mean age = 31 years **Inclusion criteria of the trial** • Women with PCOS and 20 obese controls, comparable for age and weight (BMI > 28 kg/m^2) • The diagnosis of PCOS was made according to the presence of oligomenorrhoea (less than 4 cycles in the last 6 months) or amenorrhoea (no menses in the last 6 months) and hyperandrogenism, defined by supranormal total and free T concentrations **Exclusion criteria of the trial** • Thyroid dysfunction • Type II diabetes • Concomitant cardiovascular, renal, and liver dysfunction • Cushing syndrome and disease and congenital adrenal hyperplasia • Medication < 3 months prior to study entry • Dieting Randomised N = 40 Withdrawals/losses to follow-up • 5/40 (13%); 2/20 in metformin group, 3/20 in placebo group • Non-compliance; 0/20 in metformin group, 3/20 in placebo group • Pregnancy; 2/20 in metformin group, 0/20 in placebo group Baseline data Hirsutism: 13/20 PCOS were hirsute none of the controls
Interventions	**Intervention** • Hypocaloric diet (1200 to 1400 kcal/day) + metformin 850 mg b.i.d. for 6 months (20) **Comparator** • Hypocaloric diet (1200 to 1400 kcal/day) + placebo b.i.d. for 6 months (20)

Outcomes	Assessments: (3): baseline, month 1 and 7 **Outcomes of the trial** (as reported) 1. Body height, weight, waist circumference, BMI, body fat (CT scan) * 2. Oral glucose tolerance test 3. Glucose, insulin, C peptide levels 4. LH/FSH, testosterone, DHEAS, estradiol, progesterone, SHBG, leptin * 5. Adverse events * * Denotes outcomes prespecified for this review
Notes	13/40 women were hirsute, no separate data reported for hirsute women, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2768): "The randomization schedule was generated in blocks of 4..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 2768): "...according to a double-blind design..." and "...drug and placebo were packaged and labeled according to subject number" Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by participants and investigators. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias

Pasquali 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5/40 (13%); 2/20 in metformin group, 3/20 in placebo group. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Pazos 1999

Methods	Randomised, active-controlled trial Setting Department of Endocrinology, Hospital Ramón y Cajal, Madrid, Spain Date of study Not reported. Duration of study 9 months
Participants	N = 54 screened, 39 randomised Mean age = 22 years **Inclusion criteria of the trial** • Hirsute women with idiopathic or functional ovarian hyperandrogenism **Exclusion criteria of the trial** • Adrenal hyperandrogenism Randomised N = 39 Withdrawals/losses to follow-up • 6/39 (15%); 2/13 in triptorelin + triphasic OCP group, 3/13 in CPA + triphasic OCP group, 1/13 in flutamide + triphasic OCP group • Lost to follow-up, did not comply with treatment, or had adverse effects Baseline data (mean (SEM)) BMI: triptorelin + triphasic OCP group 24.5 (1.5), CPA + triphasic OCP group 25.1 (0.9), flutamide + triphasic OCP group 23.2 (1.2) F-G score: triptorelin + triphasic OCP group 15.6 (1.8), CPA + triphasic OCP group 12.9 (1.4), flutamide + triphasic OCP group 15.8 (1.0)
Interventions	**Intervention** • Triptorelin 3.75 mg im every 28 days + triphasic OCP for 9 months (13) **Comparator 1** • Cyproterone acetate 100 mg/day on days 1 to 10 of the menstrual cycle + triphasic OCP for 9 months (13) **Comparator 2** • Flutamide 250 mg/day + triphasic OCP for 9 months (13)

Outcomes	Assessments (3): baseline, month 3 and 9 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. LH, FSH, estradiol, testosterone, SHBG, 11-deoxycortisol, 17OH progesterone, DHEA, DHEAS, androstenedione * 3. Liver function tests 4. Lipid profile 5. Adverse events * * Denotes outcomes prespecified for this review
Notes	The triphasic OCP contained ethinyl estradiol and levonorgestrel (30 µg + 0.05 mg/d on days 1 to 6, 40 µg + 0.075 mg/d on days 7 to 11, and 30 µg + 0.125 mg/d on days 11 to 21)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 123): "...were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/39 (15%); 2/13 in triptorelin + triphasic OCP group, 3/13 in CPA + triphasic OCP group, 1/13 in flutamide + triphasic OCP group. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Penna 2005

Methods	Randomised, double-blind, placebo-controlled trial Setting Gynecology Institute of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil Date of study June 2002 until May 2003. Duration of intervention 6 months
Participants	N = 30 Mean age = 26 years **Inclusion criteria of the trial** • Menstrual disorders (< 6 menstruations/12 months) • Clinical (Ferriman-Gallwey index ≥ 8) or laboratory (testosterone > 80 ng/dl and/or androstenedione > 190 ng/dl) hyperandrogenism • BMI of 30 to 40 kg/m^2 • Insulin resistance **Exclusion criteria of the trial** • Alterations with threshold values of hepatic function aspartate aminotransferase, 31 IU/l and alanine aminotransferase (GTP), 36 IU/l), alterations of renal function (creatinine, 1.3 mg/dl and urea, 40 mg/dl), alterations of thyroid function (thyroid-stimulating hormone (TSH), 5.50 mIU/ml and free thyroxin, 1.76 ng/dl) • Hyperprolactinaemia • Congenital adrenal hyperplasia • Diabetes • Use of hormonal medications or medications that might interfere with carbohydrate metabolism < 6 months prior to study entry Randomised N = 30 Withdrawals/losses to follow-up • 3/30 (10%); 2/15 in acarbose group, 1/15 in placebo group • Pregnancy; 1/15 in acarbose group, 0/15 in placebo group

	• Lost to follow-up; 1/15 in acarbose group, 1/15 in placebo group Baseline data (mean (SD)) BMI: acarbose group 35.04 (2.84), placebo group 35.87 (2.60) F-G index: acarbose group 10.29 (4.70), placebo group 8.85 (2.31) Testosterone (ng/dl): acarbose group 70.64 (29.70), placebo group 76.76 (21.16) Androstenedione (ng/dl): acarbose group 133.95 (96.13), placebo group 139.72 (63.03) SHBG (nmol/L): acarbose group 21.79 (9.31), placebo group 21.01 (7.9)
Interventions	**Intervention** • Acarbose 50 mg 3 times a day for 6 months (15) **Comparator** • Placebo 3 times a day for 6 months (15)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey index * 2. Menstrual cycles * 3. Weight, height, BMI * 4. LH, FSH, prolactin, testosterone, androstenedione, DHEAS, 17-OH progesterone, SHBG, urinary cortisol, free thyroxin, TSH, urea, creatinine, GOT and GTP * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2397): "assigned by computed randomization (GraphPad StatMate, San Diego, CA, USA)" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote (page 2397): "The medications were prepared and coded by the Industrial Pharmacy of the University Hospital of Ribeirão Preto..." Comment: form of central allocation, probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 2397): "The medications were prepared and coded by the Industrial Pharmacy of the University Hospital of

Penna 2005 (*Continued*)

		Ribeirão Preto using Glucobay (Bayer, Rio de Janeiro, RJ, Brazil) or flour and identified by codes (double-blind)." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by participants and investigators. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/30 (10%); 2/15 in acarbose group, 1/15 in placebo group Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Porcile 1991

Methods	Randomised, active-controlled trial Setting School of Medicine of the University of Chile, Hospital del Salvador, Santiago, Chile Date of study Not reported. Duration of intervention 2 years
Participants	N = 26 Mean age = 23 years **Inclusion criteria of the trial** • Idiopathic hirsutism or hirsutism in PCOS **Exclusion criteria of the trial** • Tumours of ovaries or adrenal glands • Cushing's disease • 21-hydroxylase deficiency

	• Drug induced hirsutism • Hyperprolactinaemia Randomised N = 26 Withdrawals/losses to follow-up • 2/26; (8%); 0/10 in desogestrel + EE 30 µg group, 1/6 in desogestrel + EE 50 µg group, 1/10 in CPA + EE group • Reasons unreported Baseline data (mean (SD)) Hirsutism score (Lorenzo 1970): desogestrel + EE 30 µg group 11.9 (3.0), desogestrel + EE 50 µg group 10.4 (2.4), CPA + EE group 12.0 (3.2) BMI: desogestrel + EE 30 µg group 22.5 (2.7), desogestrel + EE 50 µg group 23.5 (2.5) , CPA + EE group 23.2 (3.6)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 2 years (10) **Comparator 1** • OCP (ethinyl estradiol 50 µg + desogestrel 0.15 mg) for 2 years (6) **Comparator 2** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 2 years (10)
Outcomes	Assessments (5): baseline, month 6, 12, 18, and 24 **Outcomes of the trial** (as reported) 1. Hirsutism score (Lorenzo 1970) * 2. Serum 17-hydroxyprogesterone, DHEAS, total and free testosterone, prolactin, FSH, LH * 3. Cholesterol, HDL cholesterol, LDL cholesterol, triglycerides * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 878): "... were randomly assigned..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment,

Porcile 1991 (*Continued*)

		was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/26; (8%); 0/10 in desogestrel + EE 30 µg group, 1/6 in desogestrel + EE 50 µg group, 1/10 in CPA + EE group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Porcile 1991B

Methods	Randomised, active- and no treatment-controlled trial Setting Department of Obstetrics and Gynecology, School of Medicine of the University of Chile, Hospital del Salvador, Santiago, Chile Date of study Not reported. Duration of intervention 2 years
Participants	N = 22 Mean age = not reported **Inclusion criteria of the trial** • Hirsute women (Lorenzo 1970), previously successfully treated with OCPs **Exclusion criteria of the trial** • Androgen-producing tumours • Congenital defects of steroidogenic enzymes • Hyperprolactinaemia • Iatrogenic hirsutism

	Randomised N = 22 Withdrawals/losses to follow-up • 2/22 (9%); 0/9 in OCP every month group, 2/8 in OCP every other month group, 0/5 in the no treatment group Baseline data (mean (SEM)) Hirsutism score (Lorenzo 1970): 5.2 (0.32) Testosterone (nmol/L): 1.62 (0.19) Free testosterone (pmol/L): 5.05 (0.35)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) each month for 2 years (9) **Comparator** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) every other month for 2 years (8) **Comparator 2** • No treatment for 2 years (5)
Outcomes	Assessments (5): baseline, month 6, 12, 18, and 24 **Outcomes of the trial** (as reported) 1. Hirsutism score (Lorenzo 1970) * 2. Total and free testosterone * 3. Cholesterol, HDL cholesterol, LDL cholesterol, triglycerides * Denotes outcomes prespecified for this review
Notes	Objective was the maintenance of remission of hirsutism, any prior treatment was discontinued during 1 to 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote page 534: "...randomly assigned to one of the following three groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement

Porcile 1991B (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/22 (9%); 0/9 in OCP every month group, 2/8 in OCP every other month group, 0/5 in the no treatment group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Prezelj 1989

Methods	Randomised, active-controlled trial Setting University Medical Centre Ljubljana, Ljubljana, Yugoslavia Date of study Not reported. Duration of intervention 6 months
Participants	N = 25 Mean age = 26 years **Inclusion criteria of the trial** • Ferriman-Gallwey score > 7 • Menstrual disorders (oligomenorrhoea, amenorrhoea) • Elevated levels of at least one of the androgens determined (serum and salivary testosterone, serum androstenedione and serum DHEAS) **Exclusion criteria of the trial** • Androgen-secreting tumours • Thyroid dysfunction • Hypercorticism • Congenital adrenal hyperplasia Randomised

	N = 25 Withdrawals/losses to follow-up • 2/25 (8%); 2/15 in dexamethasone + spironolactone group, 0/10 in spironolactone group • Cushing syndrome; 1/15 in dexamethasone + spironolactone group, 0/10 in spironolactone group • Polymenorrhoea; 1/15 in dexamethasone + spironolactone group, 0/10 in spironolactone group Baseline data (median) F-G score: dexamethasone group + spironolactone 12, spironolactone group 11 Testosterone (nmol/L): dexamethasone + spironolactone group 2.3, spironolactone group 2.2 Androstenedione (nmol/L): dexamethasone + spironolactone group 10.8, spironolactone group 10.6 DHEAS (μmol/L): dexamethasone + spironolactone 8.3 group, spironolactone group 9.5
Interventions	**Intervention** • Dexamethasone 0.5 mg daily + 100 mg of spironolactone b.i.d. in 3-week cycles after 1-week intervals for 6 months (15) **Comparator** • Spironolactone 100 mg b.i.d. for 6 months (10)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. LH, FSH, prolactin, total testosterone, salivary testosterone, androstenedione, DHEAS, SHBG, estradiol, estrone * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 282): "...were randomized into two treatment groups by means of computer generated pseudo random numbers" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported

Prezelj 1989 (*Continued*)

		Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/25 (8%); 2/15 in dexamethasone + spironolactone group, 0/10 in spironolactone group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Rautio 2005

Methods	Randomised, placebo-controlled trial Setting Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland Date of study February 2002 until April 2004. Duration of intervention 4 months
Participants	N = 30 Mean age = 28 years **Inclusion criteria of the trial** • PCOS, defined as polycystic ovaries (in vaginal ultrasonography) and at least one of the following symptoms: oligomenorrhoea or amenorrhoea, clinical manifestations of hyperandrogenism, such as a hirsutism score of more than 7, according to Ferriman and Gallwey, and/or an elevated serum testosterone level (> 2.7 nmol/L) **Exclusion criteria of the trial** • Diabetes • Signs of liver or renal failure or active liver disease (alanine aminotransferase (ALT) > 2.5x the upper limit of normal values) • Smokers, alcohol users and those taking sex hormones or drugs known to affect

	lipid metabolism < 2 months prior to study entry Randomised N = 30 Withdrawals/losses to follow-up • 4/30 (13%); 3/15 in rosiglitazone group, 1/15 in placebo group • Personal reasons; 1/15 in rosiglitazone group, 1/15 in placebo group • Pregnancy; 2/15 in rosiglitazone group, 0/15 in placebo group Baseline data (mean (SEM)) BMI: rosiglitazone group 33.1 (1.7), placebo group 33.6 (1.0) Waist/hip ratio: rosiglitazone group 0.87 (0.12), placebo group 0.88 (0.01) F-G score: rosiglitazone group 8.92 (0.9), placebo group 9.86 (1.5) Testosterone (nmol/L): rosiglitazone group 2.7 (0.1), placebo group 3.5 (0.3) SHBG (nmol/L): rosiglitazone group 30.3 (3.4), placebo group 38.6 (5.3) Androstenedione (nmol/L): rosiglitazone group 16.6 (1.8), placebo group 16.3 (1.7) DHEAS (μmol/L): rosiglitazone group 8.18 (0.9), placebo group 5.2 (0.7)
Interventions	**Intervention** • Rosiglitazone 4 mg once daily for 2 weeks and then b.i.d. up to 4 months (15) **Comparator** • Placebo for 4 months (15)
Outcomes	Assessments (2): baseline, month 4 **Outcomes of the trial** (as reported) 1. Waist-hip circumference, BMI, hirsutism score * 2. Oral glucose tolerance test, intravenous glucose tolerance test 3. Euglycaemic hyperinsulinaemic clamp 4. Calorimetry 5. LH, FSH, DHEA, DHEAS, SHBG, testosterone, androstenedione, 17OH progesterone * 6. Glucose, insulin, insulin-like growth factor-binding protein-1 * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1401): "Using computer-generated assignment..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported

		Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 1401): "...blindly allocated to either a placebo group (PLA group) or a rosiglitazone group (ROSI group)..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 1401): "...blindly allocated to either a placebo group (PLA group) or a rosiglitazone group (ROSI group)..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/30 (13%); 3/15 in rosiglitazone group, 1/15 in placebo group. Per-protocol analysis Comment: moderate number of drop-outs at follow-up and per-protocol analysis; considered to be at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Rittmaster 1988

Methods	Randomised, active-controlled, cross-over trial Setting Division of Endocrinology and Departments of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada Date of study Not reported. Duration of intervention 4 months
Participants	N = 8 Mean age = 25 years **Inclusion criteria of the trial** • Idiopathic hirsutism **Exclusion criteria of the trial** • Ovarian or adrenal neoplasm • Cushing's syndrome • Attenuated or classical congenital adrenal hyperplasia • Drug-induced hirsutism Randomised N = 8 Withdrawals/losses to follow-up • No losses to follow-up Baseline data Individual participant data are provided, no means
Interventions	**Intervention** • Prednisone 100 µg/kg each night orally for 4 months (4) and then was switched to the other schedule for 4 months **Comparator** • Prednisone 200 µg/kg every other night orally for 4 months (4) and then was switched to the other schedule for 4 months
Outcomes	Assessments (4): baseline, month 4 and 8 at 2 successive days **Outcomes of the trial** (as reported) 1. Serum cortisol, DHEA, androstenediol glucuronide * *Denotes outcomes prespecified for this review
Notes	No wash-out period between treatment schedules, no separate end data/baseline data at 4 months, no data on hirsutism score, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 400): "...randomly assigned to ..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable

Rittmaster 1988 (*Continued*)

		groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 400): "This work was supported by Grant MA-9619 from the Medical Research Council of Canada and a grant from the Dalhousie University Internal Medicine Research Foundation" Comment: we judged this as at a low risk of bias

Rittmaster 1990

Methods	Randomised, placebo-controlled trial Setting Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada Date of study Not reported. Duration of intervention 4 months
Participants	N = 20 Mean age = 31 years **Inclusion criteria of the trial**

	• Moderate to severe hirsutism (modified Ferriman-Gallwey score > 10) • 18 to 40 years **Exclusion criteria of the trial** • Ovarian or adrenal neoplasm • Prolactinoma • Cushing's syndrome • Homozygous congenital adrenal hyperplasia • Drug-induced hirsutism • Medical therapy for hirsutism or other medications known to influence hormone levels < 3 months prior to study entry Randomised N = 20 Withdrawals/losses to follow-up • 2/20 (10%); 1/10 in dexamethasone group, 1/10 in placebo group • Adverse effects; 1/10 in dexamethasone group, 1/10 in placebo group Baseline data (mean (SD)) Modified F-G score: idiopathic hirsutism 26 (7), PCOS 27 (6) BMI: idiopathic hirsutism 34 (8), PCOS 33 (7)
Interventions	**Intervention** • Leuprolide + dexamethasone 0.5 mg/day for 4 months (10) **Comparator** • Leuprolide + placebo for 4 months (10)
Outcomes	Assessments (2): baseline and month 4 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Testosterone, DHEAS, androstenediol glucuronide, LH, FSH, cortisol * 3. Mean vertebral density * Denotes outcomes prespecified for this review
Notes	2-phase study: first phase all participants received leuprolide for 5 to 6 months before they were randomised for second phase and received dexamethasone or placebo in addition to leuprolide. However, in the first phase the first 10 women were part of a dose response study, while the second 10 received a fixed-dose leuprolide. No wash-out phase. No baseline data for second phase per treatment arm. Data are provided for idiopathic hirsutism and PCOS, but not clear per treatment arm. Protocol deviation biasing therapeutic comparisons in addition to inconsistency and incompleteness in outcome reporting did not permit a clear analysis and interpretation of results. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1097): "...were randomized to ..." Comment: insufficient detail was reported

		about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 1097): "...initially double blind, but because of side-effects in all but 1 woman receiving dexamethasone, blinding became impossible..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 1097): "...initially double blind, but because of side-effects in all but 1 woman receiving dexamethasone, blinding became impossible..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/20 (10%); 1/10 in dexamethasone group, 1/10 in placebo group Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 1096 and 1102): "This work was supported by Grant MA-9319 from the Medical Research Council of Canada and a grant from the Dalhousie University Internal Medicine Research Foundation." and "We are indebted to Dr. Claude Auclair and Abbott Laboratories, Canada, for supplying leuprolide."

		Comment: we judged this as at a low risk of bias

Roth 2012

Methods	Randomised, double-blind, active-controlled trial Setting Multi-centre (12) worldwide Date of study November 2002 until December 2004. Duration of intervention 6 months
Participants	N = 626 Mean age = 28 years **Inclusion criteria of the trial** • Hirsute women with PCOS, with a Ferriman-Gallwey score > 8 **Exclusion criteria of the trial** • Not reported Randomised N = 626 Withdrawals/losses to follow-up • 121/626 (19%) were not hirsute; 44/209 in clomiphene group, 36/208 in metformin group, 41/209 in combination group Baseline data (mean (SD)) BMI: clomiphene group 36.9 (9.0), metformin group 36.1 (8.3), combination group 35.0 (8.0) F-G score: clomiphene group 17.3 (7.1), metformin group 16.4 (7.1), combination group 16.8 (6.1) SHBG (nmol/L): clomiphene group 29.5 (19.3), metformin group 26.0 (13.9), combination group 29.4 (18.5) Total testosterone (ng/dl): clomiphene group 64.2 (34.2), metformin group 63.4 (26.0) , combination group 66.1 (29.3)
Interventions	**Intervention** • Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle for 6 cycles (209) **Comparator 1** • Metformin 1000 mg b.i.d. (starting at lower dosage) for 6 cycles (208) **Comparator 2** • Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle + metformin 1000 mg b.i.d. (starting at lower dosage) for 6 cycles (209)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Progesterone levels 2. Ferriman-Gallwey score * 3. Total testosterone, SHBG, free androgen index * *Denotes outcomes prespecified for this review

Notes	No further drop-outs were reported in this study whereas Legro 2007 (secondary reference under this study) which focused on treating infertility did report losses to follow-up. Roth 2012 only included some of the participants included in Legro 2007, so it is unclear what the number of drop-outs were in this subset. In analysing the data from this study we have only included hirsute participants (clomiphene group N = 165, metformin group N = 172 and the combo group N = 168)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 1152): "...randomized by means of an interactive voice system to blindly receive standard clomiphene citrate treatment..." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1152): "...randomized by means of an interactive voice system to blindly receive standard clomiphene citrate treatment...", form of central allocation Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (see Legro, under primary reference page 552): "...Extended-release metformin (Glucophage XR) plus identical placebo were provided by Bristol-Myers Squibb. Overencapsulated clomiphene citrate tablets (purchased from Teva Pharmaceuticals) and matching placebo capsules were packaged and tested by a commercial pharmacy supply company (CTS) specifically for the study. Neither manufacturer had any other role in the study." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were investigator-assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias

Incomplete outcome data (attrition bias) All outcomes	High risk	121/626 (19%); 55/209 in clomiphene group, 72/208 in metformin group, 49/209 in combination group. Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 1151): "Supported by National Institutes of Health/National Institute of Child Health and Human Development... etc" and "The other authors did not report any potential conflicts of interest." Comment: we judged this as at a low risk of bias

Sabuncu 2003

Methods	Randomised, active-controlled trial Setting Endocrinology and Gynaecology outpatient clinics of the University of Harran, Faculty of Medicine, Research Hospital, Sanliurfa, Turkey Date of study Not reported. Duration of intervention 6 months
Participants	N = 40 Mean age = 28 years **Inclusion criteria of the trial** • Obese patients with PCOS • PCOS defined as a combination of oligomenorrhoea (6 or fewer menses per year) and hyperandrogenism - elevated serum total testosterone or free testosterone concentrations. In the vaginal ultrasonographic examination, all the patients had ovaries consistent with a diagnosis of PCOS: presence of multiple subcapsular follicles during the first 3 days of menstrual bleeding. The modified Ferriman-Gallwey hirsutism score was > 8 in all patients **Exclusion criteria of the trial** • Pregnancy • Diabetes mellitus • Hypertension • Liver, renal failure, or thyroid dysfunction

	• Drug or vitamin treatment • Smoking or alcohol < 3 months prior to study entry • Other causes of hirsutism and hyperandrogenism derived from the pituitary, adrenals, or ovaries, such as prolactinoma, Cushing's syndrome, congenital adrenal hyperplasia, and androgen-secreting tumours Randomised N = 40 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SD)) BMI: EE/CPA group 37.8 (6.1), sibutramine group 37.5 (5.0), combination group 37.7 (5.8) F-G score: EE/CPA group 14.3 (3.9), sibutramine group 13.3 (3.7), combination group 13.4 (3.8) Waist/hip ratio: EE/CPA group 0.83 (0.07), sibutramine group 0.83 (0.08), combination group 0.83 (0.06) Total testosterone (ng/dl): EE/CPA group 133.3 (27.2), sibutramine group 135.9 (23.6), combination group 134.4 (30.5) Free testosterone (ng/dl): EE/CPA group 4.2 (1.0), sibutramine group 4.3 (0.9), combination group 4.3 (1.1) SHBG (nmol/L): EE/CPA group 19.6 (14.4), sibutramine group 17.5 (11.5), combination group 17.7 (11.6) DHEAS (µg/dl): EE/CPA group 257.4 (86.9), sibutramine group 252.9 (85.6), combination group 254.6 (107.2)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (14) **Comparator 1** • Sibutramine 10 mg/day for 6 months (12) **Comparator 2** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + sibutramine 10 mg/day for 6 months (14) Additionally, all patients were given a diet of 1200 kcal, and group 2 patients were advised to use barrier contraception to avoid pregnancy during the study period
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Oral glucose tolerance test, AUC glucose, AUC insulin 2. Weight, height, BMI, waist/hip ratio * 3. Serum glucose, serum insulin, total cholesterol, HDL and LDL cholesterol, and triglyceride 4. Total testosterone, free testosterone, DHEAS, SHBG * *Denotes outcomes prespecified for this review
Notes	-
Risk of bias	

Sabuncu 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1199): "...randomized..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Saeed 1993

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Obstetrics and Gynaecology, Allama Iqbal Medical College, Lahore, Pakistan Date of study Not reported. Duration of intervention 1 year
Participants	N = 20 Mean age = 21 years **Inclusion criteria of the trial** • PCOS, defined as oligo or amenorrhoea and hirsutism (Ferriman-Gallwey score > 8) **Exclusion criteria of the trial** • Other endocrine or metabolic disorders • Contraindication for OCP Randomised N = 20 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data Individual participant data are provided, no means
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 1 year (10) **Comparator** • Placebo for 1 year (10) Participants were advised barrier contraception techniques, and participants in both groups were prescribed local cosmetic therapy like electrolysis, bleaching agents or shaving
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Subjective assessment of hirsutism; 3-point Likert scale * 2. Objective assessment of hirsutism (increase of terminals hairs, reduced speed in hair growth, less pigmentation, disappearance of unwanted hair) * 3. Testosterone, DHEAS, FSH, LH * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 110): "...randomly allocated. .." Comment: insufficient detail was reported

		about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 110): "... in a double-blind manner..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 110): "... in a double-blind manner..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	High risk	Objective assessment of hirsutism was a prespecified outcome but not reported. Nor were data provided on hormone assessments in the placebo group Comment: we judged this as at a high risk of bias
Other bias	High risk	Quote (page 110): "patients in both groups were prescribed local cosmetic therapy like electrolysis, bleaching agents or shaving" Comment: these interventions hamper the assessment of hirsutism and although this occurred in both groups, we judged this as at high risk of bias

Sahin 1998

Methods	Randomised, active-controlled trial Setting Departments of Obstetrics and Gynecology and Endocrinology, Erciyes University, Faculty of Medicine, Kayseri, Turkey Date of study Not reported. Duration of intervention 9 months
Participants	N = 42 Mean age = 22 years **Inclusion criteria of the trial** • Hirsute women **Exclusion criteria of the trial** • Androgen-secreting tumours of ovarian or adrenal origin • Cushing's syndrome • Thyroid dysfunction • 21-hydroxylase deficiency • Hyperprolactinoma Randomised N = 42 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: EE/CPA group 22.74 (1.95), finasteride group 25.54 (1.61) Modified F-G score: EE/CPA group 15.81 (1.19), finasteride group 17.81 (1.05) Free testosterone (pg/ml): EE/CPA group 3.68 (0.42), finasteride group 3.34 (0.38) DHEAS (µg/dl): EE/CPA group 297 (23), finasteride group 306 (33) SHBG (nmol/L): EE/CPA group 36.95 (3.92), finasteride group 34.95 (3.61) PCOS: EE/CPA group 9/21, finasteride group 9/21 Idiopathic hirsutism: EE/CPA group 12/21, finasteride group 12/21
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 9 months (21) **Comparator** • Finasteride 5 mg daily for 9 months (21)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Free testosterone, total testosterone, DHEAS, androstenedione, SHBG * 2. Modified Ferriman-Gallwey score * 3. Haematologic screening and hepatic and renal function * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Sahin 1998 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 349): "...were randomized into two groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Hirsutism was assessed by the same investigator blinded to treatment. The other outcomes are not likely to be influenced by the lack of blinding (serum tests) Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	High risk	Measurements of total testosterone and androstenedione were prespecified outcomes but not reported Comment: we judged this as at a high risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Sanam 2011

Methods	Randomised, active-controlled trial Setting Amir Hospital Family Planning Clinic and some health centres in Semnan, Iran Date of study October 2007 until October 2008. Duration of intervention 6 months
Participants	N = 100 Mean age = 26 years **Inclusion criteria of the trial** • Healthy women of reproductive age **Exclusion criteria of the trial** • Contraindication OCP • Hormonal treatment such as "Norplant", depot medroxyprogesterone acetate, or OCP < 6 months prior to study entry • Lack of co-operation • Irregular consumption of the pills • Pregnancy during study • Prolonged and uncontrollable abnormal uterine bleeding Randomised N = 100 Withdrawals/losses to follow-up • 9/100 (9%); 5/50 in EE/desogestrel group, 4/50 in EE/levonorgestrel group • Post-randomisation exclusions as those did not match the inclusion criteria Baseline data (mean (SD)) BMI: EE/desogestrel group 25.7 (4.1), EE/levonorgestrel group 25.0 (5.7) F-G score: EE/desogestrel group 2.5 (4.3), EE/levonorgestrel group 2.7 (4.4)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 6 months (50) **Comparator** • OCP (ethinyl estradiol 30 µg + levonorgestrel 0.15 mg) for 6 months (50)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Number of acne lesions * 3. Free testosterone, SHBG * * Denotes outcomes prespecified for this review
Notes	The mean of the F-G score as reported does not match the recognised minimum criteria for hirsutism (score > 8; Hatch 1981). No separate data for hirsute women, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 24): "... randomly given...", "...for this purpose a random number table was used..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/100 (9%); 5/50 in EE/desogestrel group, 4/50 in EE/levonorgestrel group. Post-randomisation exclusions for not meeting the inclusion criteria. Per-protocol analysis Comment: low number of drop-outs and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Although one of the principal aims of the study was the effect of the interventions on hirsutism, the mean Ferriman-Gallwey score of the participants was between 2 and 3. Hirsutism in women: minimum Ferriman-Gallwey score of 8 (Hatch 1981)

Sathyapalan 2012

Methods	Randomised, double-blind, placebo-controlled trial Setting Department of Diabetes, Endocrinology and Metabolism, Hull York Medical School, Hull, UK Date of study January 2006 until December 2007. Duration of intervention 3 months
Participants	N = 40 Mean age = 28 years **Inclusion criteria of the trial** • PCOS based on all 3 diagnostic criteria of Rotterdam Criteria PCOS 2004: Ferriman-Gallwey score > 8, free androgen index > 8, oligomenorrhoea, amenorrhoea, and polycystic ovaries on ultrasound **Exclusion criteria of the trial** • Concurrent diseases • Medication affecting insulin sensitivity, lipids, or ovarian function including OCPs < 6 months prior to study entry • Non classical 21-hydroxylase deficiency • Hyperprolactinaemia • Cushing's disease • Androgen secreting tumours Randomised N = 40 Withdrawals/losses to follow-up • 3/40 (8%); 1/20 in atorvastatin group, 2/20 in placebo group for non-compliance Baseline data (mean (SD)) BMI: atorvastatin group 33.20 (1.4), placebo group 33.92 (1.4) DHEAS (µmol/L): atorvastatin group 7.1 (1.0), placebo group 7.2 (1.2) Androstenedione (nmol/L): atorvastatin group 5.7 (0.8), placebo group 5.6 (1.3)
Interventions	**Intervention** • Atorvastatin 20 mg for 3 months (20) **Comparator** • Placebo for 3 months (20) Afterwards al participants received metformin 500 mg 3 times a day for 3 months
Outcomes	Assessments (2): baseline and month 3 **Outcomes of the trial** (as reported) 1. Change in androstenedione and DHEAS * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Sathyapalan 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote (page 81): "...were randomly assigned...computer-generated randomization list." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote (page 81): "Labelling was done by personnel not involved in the trial" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 81): "double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 81): "double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study. However, measurements (serum tests) are unlikely to be influenced by lack of blinding. We judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/40 (8%); 1/20 in atorvastatin group, 2/20 in placebo group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Schmidt 1987

Methods	Randomised, active-controlled trial Setting Department of Dermatology and Gynecology, University of Vienna, Austria Date of study Not reported. Duration of intervention 9 months
Participants	N = 20 Mean age = 29 years **Inclusion criteria of the trial** • Women with moderate to severe hirsutism **Exclusion criteria of the trial** • Not reported Randomised N = 20 Withdrawals/losses to follow-up • 5/20 (25%); 0/10 in CPA im group, 5/10 in CPA oral group • "Technical reasons"; 0/10 in CPA im group, 5/10 in CPA oral group Baseline data (mean) Initial hair diameter (chin, micrometer): CPA im group 0.0757, CPA oral group 0.0835
Interventions	**Intervention** • Cyproterone acetate 300 mg parenterally implant first day of each cycle for 9 months (10) **Comparator** • Cyproterone acetate 100 mg/day orally for first 10 days of the cycle for 9 months (10)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Hair-diameter; micrometer * 2. Dermatological criteria for hair overgrowth 3. Androstenedione, DHEAS, prolactin * 4. Adverse events * * Denotes outcomes prespecified for this review
Notes	Inconsistent data reporting, lack of clarity about missing outcome data and withdrawals and losses. See Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 126): "Patients were allotted to the two regimens at random." Comment: insufficient detail was reported about the method used to generate the allo-

Schmidt 1987 (*Continued*)

		cation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	5/20 (25%); 0/10 in CPA im group, 5/10 in CPA oral group. Per-protocol analysis Comment: the high and unbalanced drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Smith 2006

Methods	Randomised, double-blind, within-participant, active-controlled trial Setting 2 centres in the US Date of study Not reported. Duration of study 34 weeks
Participants	N = 64 Mean age = 47 years **Inclusion criteria of the trial**

	• Fitzpatrick skin types I through IV • Bilaterally symmetric facial hirsutism of the lip and chin with predominantly brown/black terminal hairs, and a hair density of 5 hairs/cm^2 in selected target areas **Exclusion criteria of the trial** • Pregnant or lactating women • Previous laser photo epilation within 6 months or electrolysis or other epilation methods < 2 months before the start of the study • Systemic medications that could affect hair growth < 6 months prior to study entry Randomised N = 64 Withdrawals/losses to follow-up • 10/64 (16%) • Voluntary withdrawal; 2/64 • Lost to follow-up; 4/64 • Protocol violation; 4/64 Baseline data Fitzpatrick skin type I 6/54, skin type II 11/54, skin type III 27/54 and skin type IV 10/54
Interventions	**Intervention** • Laser therapy (Nd: YAG or alexandrite) at week 2 and 10 + eflornithine cream for 34 weeks **Comparator** • Laser therapy (Nd: YAG or alexandrite) at week 2 and 10 + vehicle cream for 34 weeks
Outcomes	Assessments (8): baseline, week 2, 6, 10, 16, 22, 28, and 34 **Outcomes of the trial** (as reported) 1. Physician's global assessment of change from baseline for right and left side (chin and upper lip); 4-point Likert scale * 2. Physician's comparison of appearance of left versus right side * 3. Subject's self assessment comparing left versus right sides * 4. Adverse events * * Denotes outcomes prespecified for this review
Notes	Eflornithine cream was used as add-on therapy to laser therapy and therefore we included the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1238): "Assignment of medications was determined via a computer-

		generated randomization schedule." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement After e-mail communication: "Prior to the start of the study, the medication container assignments for EACH subject number were placed into sealed envelopes marked with subject numbers." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1238): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "The study medication containers did NOT reveal whether the product inside was active or placebo and the numbers were different for each study container. The actual treatment assignments were maintained by an off-site study administrator not directly related to the site thus the site did not have regular access to the treatment assignments and could only obtain that information through a formal unblinding process. Participants (via the staff) received medication containers that contained either the active medication or a placebo vehicle prepared by the medication manufacturer that matched the active product in colour, feel and odour." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 1238): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study. However, measurements (serum tests) are unlikely to be influenced by lack of blinding. We judged this as at low risk of bias After e-mail communication: see 'performance bias' domain Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/64 (16%), reasons reported. Both per-protocol and intention-to-treat analyses were undertaken and stated to be "similar" but only per-protocol analyses were presented Comment: moderate number of losses posed an unclear risk of bias for this domain
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 1237): "An unrestricted educational grant was received from Bristol-Myers Squibb Inc. Laser equipment was provided for the duration of the study only by Laserscope Corp. and Candela Corp." Comment: we judged this as at a low risk of bias

Sobbrio 1990

Methods	Randomised, open, active-controlled trial Setting Institute of Clinica Medica and Institute of Gynecology, University of Messina, School of Medicine, Messina, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 34 Age range: 18 to 32 years **Inclusion criteria of the trial** • Non-obese hirsute women with micro polycystic ovary syndrome (MPCOS) **Exclusion criteria of the trial** • Oral medication < 6 months prior to study entry Randomised N = 34 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) F-G score: EE/desogestrel 21.4 (7.5), EE/gestodene 19.7 (8.7) Testosterone (ng/ml): EE/desogestrel 0.77 (0.21), EE/gestodene 0.88 (0.29) Free testosterone (pg/ml): EE/desogestrel 3.52 (1.48), EE/gestodene 2.96 (1.04) Androstenedione (ng/ml): EE/desogestrel 3.21 (1.50), EE/gestodene 2.69 (1.47) DHEAS (µg/dl): EE/desogestrel 306 (178), EE/gestodene 282 (119) SHBG (nmol/L): EE/desogestrel 35 (17), EE/gestodene 38 (12)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + desogestrel 0.15 mg) for 6 months (17) **Comparator** • OCP (ethinyl estradiol 30 µg + gestodene 75 µg) for 6 months (17)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Total and free testosterone, androstenedione, DHEA, DHEAS, 17-OH progesterone, SHBG, ceruloplasmin, FAI * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 140): "...in two randomized groups..." Comment: insufficient detail was reported about the method used to generate the allo-

Sobbrio 1990 (*Continued*)

		cation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 139): "...open..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 139): "...open..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Spritzer 2000

Methods	Randomised, active-controlled trial Setting Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil Date of study Not reported. Duration of intervention 12 months
Participants	N = 46 Age = 24 years **Inclusion criteria of the trial** • Hirsute women with PCOS and idiopathic hirsutism • The diagnosis of PCOS was based on the physical features of hyperandrogenism,

	disturbed menstrual cycles, elevated serum LH levels or LH/FSH ratio, increased levels of serum testosterone and/or androstenedione and no evidence of ovarian or adrenal neoplasm or Cushing's syndrome. The diagnosis of PCOS followed NIH consensus criteria (Zawadski 1992) **Exclusion criteria of the trial** • Late-onset (non-classic) congenital adrenal hyperplasia • Hyperprolactinaemia • Drugs known to interfere with hormonal levels < 3 months prior to study entry Randomised N = 46 Withdrawals/losses to follow-up • 2/46 (4%); lost to follow-up unclear from which group Baseline data (mean (SEM)) F-G score PCOS group: spironolactone group 22 (2), CPA group 21 (1) F-G score idiopathic hirsutism group: spironolactone group 21 (2), CPA group 23 (2) Testosterone PCOS group (nmol/L): spironolactone group 3.05 (0.45), CPA group 2.94 (0.38) Testosterone idiopathic hirsutism group (nmol/L): spironolactone group 2.35 (0.41), CPA group 2.25 (0.31) Androstenedione PCOS group (nmol/L): spironolactone group 11.62 (2.16), CPA group 11.41 (1.39) Androstenedione idiopathic hirsutism group (nmol/L): spironolactone group 8.65 (0.76), CPA group 10.48 (0.94)
Interventions	**Intervention** • Spironolactone 200 mg/day for 12 months (21 = N that completed the study) **Comparator** • Cyproterone acetate 50 mg/day 20 days per month + ethinyl estradiol 35 µg over the last 10 days for 12 months (23 = N that completed the study)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. LH, testosterone, androstenedione * 3. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 588): "...subjects were randomly separated into two treatment groups and stratified for the presence of PCOS"

		Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/46 (4%); lost to follow-up unclear from which group. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 592): "This study was supported by grants from Financiadora de Estudos e Projetos (no. 41960949.00), Conselho Nacional de Desenvolvimento Científicoco e Tecnológico (no. 520544/960-0) and Fundação de Amparo à Pesquisa do Rio Grande do Sul (no. 96/1765.7)." Comment: we judged this as at a low risk of bias

Spuy 1995

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynaecology, University of Cape Town, Cape Town, South Africa Date of study Not reported. Duration of intervention up to 52 weeks
Participants	N = 34 Mean age = not reported **Inclusion criteria of the trial** • Hirsute women with PCOS **Exclusion criteria of the trial** • Not reported Randomised N = 34 Withdrawals/losses to follow-up • 6/34 (18%); unclear from which group Baseline data Nothing reported
Interventions	**Intervention** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) for 52 weeks **Comparator** • OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) + GnRH agonist analogue (goserelin) for 52 weeks
Outcomes	Assessments: baseline and at end of study, other assessments unclear **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Sebum scores 3. Testosterone, androstenedione, DHEAS, SHBG, estradiol, estrone and FAI * *Denotes outcomes prespecified for this review
Notes	Abstract from conference proceedings, limited data reported, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 242): "...randomly allocated. .." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6/34 (18%); unclear from which group. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

Stener-Victorin 2009

Methods	Randomised, active- and no treatment controlled trial Setting Sahlgrenska University Hospital, Göteborg, Sweden Date of study November 2005 until January 2008. Duration of study 16 weeks
Participants	N = 504 recruited, 84 randomised Mean age = 30 years **Inclusion criteria of the trial** • Women with PCOS • PCOS defined as polycystic ovaries (at least 12 follicles, 2 mm to 9 mm); and/or increased ovarian volume (10 ml) revealed by two-dimensional ultrasound examinations in one or both ovaries, together with one of the following clinical symptoms: oligomenorrhoea with intermenstrual interval 35 days, and/or clinical and/or biochemical signs of hyperandrogenism (hirsutism or acne), according to the Rotterdam consensus report (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Women on medication(s) < 3 months prior to study entry

	• Breast feeding 6 months prior to study entry • Known endocrine or neoplastic causes of hyperandrogenaemia including androgen-secreting tumours, Cushing's syndrome, congenital adrenal hyperplasia and hyperprolactinaemia Randomised N = 84 Withdrawals/losses to follow-up • 10/84; 4/33 in low-frequency electro-acupuncture group, 4/34 in physical exercise group, 2/17 in the untreated control group • Moved from area; 3/33 in low-frequency electro-acupuncture group, 0/34 in physical exercise group, 1/17 in the untreated control group • Personal reasons; 1/33 in low-frequency electro-acupuncture group, 3/34 in physical exercise group, 1/17 in the untreated control group • Pregnancy; 0/33 in low-frequency electro-acupuncture group, 1/34 in physical exercise group, 0/17 in the untreated control group • Of the remaining 74 participants, 23 were randomly recruited for microneurography and nerve recordings were successfully performed in 20 women Baseline data on the 20 women in which nerve recordings have been performed (mean (SD)) BMI: low-frequency electro-acupuncture group 27.5 (8.6), physical exercise group 26.8 (4.8), untreated control group 28.0 (6.2) F-G score: low-frequency electro-acupuncture group 16.1 (8.5), physical exercise group 12.8 (10.1), untreated control group 9.5 (5.1)
Interventions	**Intervention** • Low-frequency electro-acupuncture for 16 weeks according to a schedule that ranged from two per week to once every two weeks (33) **Comparator 1** • Physical exercise 30 to 45 minutes at least 3 times a week for 16 weeks (34) **Comparator 2** • Untreated for 16 weeks (17)
Outcomes	Assessments (2): baseline and week 16 **Outcomes of the trial** (as reported) 1. BMI, sagittal abdominal diameter, waist/hip ratio * 2. Ferriman-Gallwey score * 3. LH, FSH, total testosterone, free testosterone, DHEAS, SHBG, FAI, free thyroxin 4, insulin growth factor 1, insulin, TSH, cholesterol, HDL and LDL cholesterol, HOMA * 4. Microneurography *Denotes outcomes prespecified for this review
Notes	Only data reported for 20/84 participants (24%), see Table 3
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page R388): "The randomization was performed by the study coordinator according to a computerized list. PCOS women were stratified by age and body mass index (BMI) and thereafter block randomized to one of three study groups in a 2:2:1 ratio:..." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 388): "This was a randomized controlled trial with independent observers and with blind, independent analysis" Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	10/84; 4/33 in low-frequency electroacupuncture group, 4/34 in physical exercise group, 2/17 in the untreated control group, reasons reported. Of the remaining 74 participants, 23 were randomly recruited for microneurography and nerve recordings were successfully performed in 20 women. Data reported for only 20/84 (24%) Comment: we judged this as at a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section

		appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page R393): "This study was supported by the Swedish Medical Research Council..., Novo Nordisk Foundation, Wilhelm and Martina Lundgrens' Science Fund, Hjalmar Svensson Foundation, Tore Nilson Foundation, Åke Wiberg Foundation, Adlerbert Research Foundation, Ekhaga Foundation, the Swedish federal government under the letters of understanding agreement of Medical Education ..., and a Regional Research and Development agreement..." Comment: we judged this as at a low risk of bias

Taheripanah 2010

Methods	Randomised, active-controlled trial Setting Infertility and Reproductive Health Research Center (IRHRC), Imam Hossein Hospital, Tehran, Iran Date of study February 2007 until December 2007. Duration of intervention 3 months
Participants	N = 60 Mean age = 23 years **Inclusion criteria of the trial** • Hirsute women with PCOS (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Hormone therapy < 3 months prior to study entry • Diet or herbal treatment • Hyperprolactinaemia • Thyroid disorders • Ovarian tumours • Cushing's disease Randomised N = 60 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) BMI: OCP group 21.17 (2.06), CPA/EE group 21.73 (2.76) F-G score: OCP group 10.78 (2.4), CPA/EE group 11.5 (2.3) Free testosterone (ng/ml): OCP group 2.48 (1.3), CPA/EE group 2.0 (1.2) DHEAS (µg/ml): OCP group 2.36 (1.6), CPA/EE group 2.41 (1.2)

Interventions	**Intervention** • OCP not specified for 3 months (30) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 3 months (30)
Outcomes	**Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Serum PSA, free testosterone, DHEAS, 17-OH progesterone * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 160): "...were divided randomly into two treatment groups according to the computer-based table" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported

Taheripanah 2010 (*Continued*)

		Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Tartagni 2000

Methods	Randomised, single-blinded, active-controlled trial Setting Università di Bari, Policlinico di Bari, Bari, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 50 Mean age = 23 years **Inclusion criteria of the trial** • Premenopausal women with severe hirsutism • Idiopathic hirsutism or hirsutism in PCOS **Exclusion criteria of the trial** • OCP or other long-term drugs < 6 months prior to study entry • Diet Randomised N = 50 Withdrawals/losses to follow-up • 4/50 (8%); 2/25 in EE/CPA group, 2/25 in EE/CPA + finasteride group for personal reasons Baseline data (mean (SD)) BMI: EE/CPA group 22 (5.6), EE/CPA + finasteride group 21.6 (8.3) Modified F-G score: 22.4 (4.7) for all included women Baseline hormone levels for women with idiopathic hirsutism (mean (SD)) Free testosterone (pg/ml): EE/CPA group 3.5 (1.1), EE/CPA + finasteride group 3.6 (0.1) Dihydrotestosterone (ng/dl): EE/CPA group 45.9 (6.1), EE/CPA + finasteride group 46.7 (5.2) DHEAS (µg/ml): EE/CPA group 3.1 (1.5), EE/CPA + finasteride group 2.5 (1.1) SHBG (µg/ml): EE/CPA group 2.4 (1.5), EE/CPA + finasteride group 3.1 (2.1) Androstenedione (ng/ml): EE/CPA group 1.8 (1.0), EE/CPA + finasteride group 2.1 (0.8) Baseline hormone levels for women with PCOS (mean (SD)) Free testosterone (pg/ml): EE/CPA group 3.8 (1.9), EE/CPA + finasteride group 4.5 (1.8) Dihydrotestosterone (ng/dl): EE/CPA group 42.0 (1.8), EE/CPA + finasteride group 40.0 (2.1) DHEAS (µg/ml): EE/CPA group 4.1 (1.0), EE/CPA + finasteride group 3.9 (1.2) SHBG (µg/ml): EE/CPA group 1.9 (1.4), EE/CPA + finasteride group 2.1 (1.4) Androstenedione (ng/ml): EE/CPA group 3.8 (1.0), EE/CPA + finasteride group 4.2 (1.6)

Tartagni 2000 (*Continued*)

Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (25) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + finasteride 5 mg once a day on day 1 to 14 for 6 months (25)
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. LH, FSH, free testosterone, DHT, DHEAS, androstenedione, 3αdiol G * 3. Self evaluation; 4 point Likert scale * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 719): "Patients were randomly assigned to two treatment groups on the basis of a computer-generated randomization sequence" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 719): "The score evaluation was performed by a single physician who was unaware of the treatment." Results of serum tests are unlikely to be influenced by the lack of blinding Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) and the lack of blind-

Tartagni 2000 (*Continued*)

		ing of participants for certain outcomes (adverse events and self evaluation of hirsutism) poses a high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/50 (8%); 2/25 in EE/CPA group, 2/25 in EE/CPA + finasteride group for personal reasons. Per-protocol analysis Comment: low number of drop-outs at follow-up and, although per-protocol analysis, considered to be at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Tartagni 2004

Methods	Randomised, single-blinded, active-controlled trial Setting Ostetrica e Ginecologica III, Universitá di Bari, Policlinico di Bari, Bari, Italy Date of study Not reported. Duration of intervention 10 months
Participants	N = 38 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute premenopausal women • Idiopathic hirsutism or hirsutism in PCOS **Exclusion criteria of the trial** • OCP or other long-term drugs < 6 months prior to study entry • Hypocaloric diet Randomised N = 38 Withdrawals/losses to follow-up • No losses to follow-up Baseline data in participants with idiopathic hirsutism (mean (SD)) BMI: finasteride every day group 22.9 (4), finasteride every 3 days group 22.5 (4) Modified F-G score: finasteride every day group 18.5 (1.9), finasteride every 3 days group 19.1 (1.6) Total testosterone (ng/dl): finasteride every day group 71.1 (1.8), finasteride every 3 days group 70.9 (2.5) Dihydrotestosterone (ng/dl): finasteride every day group 46.4 (0.3), finasteride every 3

	days group 45.7 (0.4) DHEAS (µg/ml): finasteride every day group 3.2 (1.4), finasteride every 3 days group 2.5 (1.5) SHBG (µg/ml): finasteride every day group 2.3 (1.6), finasteride every 3 days group 2.9 (2.0) Androstenedione (ng/ml): finasteride every day group 1.9 (1.1), finasteride every 3 days group 2.3 (0.7) Baseline data in participants with PCOS (mean (SD)) BMI: finasteride every day group 25.1 (4.2), finasteride every 3 days group 24.9 (4.4) Modified F-G score: finasteride every day group 20.6 (2.6), finasteride every 3 days group 21.0 (1.3) Total testosterone (ng/dl): finasteride every day group 76.8 (2.7), finasteride every 3 days group 77.5 (2.1) Dihydrotestosterone (ng/dl): finasteride every day group 40.9 (1.7), finasteride every 3 days group 40.5 (1.4) DHEAS (µg/ml): finasteride every day group 4.0 (1.1), finasteride every 3 days group 3.8 (1.1) SHBG (µg/ml): finasteride every day group 1.8 (1.2), finasteride every 3 days group 2.1 (1.6) Androstenedione (ng/ml): finasteride every day group 3.6 (1.1), finasteride every 3 days group 4.0 (1.2)
Interventions	**Intervention** • Finasteride 2.5 mg/day for 10 months (19) **Comparator** • Finasteride 2.5 mg/day every 3 days for 10 months (19)
Outcomes	Assessments (3): baseline, month 5 and 10 **Outcomes of the trial** (as reported) 1. BMI * 2. Hirsutism score (modified Ferriman-Gallwey score) * 3. Adverse effects * 4. Liver and renal function tests, triglycerides, total cholesterol, HDL and LDL cholesterol, glucose 5. FSH, LH, total testosterone, DHT, DHEAS, androstenedione, 3αdiol G, estradiol * 6. Self evaluation; 4-point Likert scale * 7. Menstrual cycle characteristics * *Denotes outcomes prespecified for this review
Notes	-
Risk of bias	

Tartagni 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 752): "The patients were randomized by a computer-generated sequence into two groups of 19 patients" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 752): "Hirsutism was scored by means of a modified Ferriman-Gallwey scoring system by a single physician who was unaware of the treatment". Serum tests are not likely to be influenced by the lack of blinding Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) and the lack of blinding of participants for certain outcomes (adverse events and self evaluation of hirsutism) poses a high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Tiitinen 1994

Methods	Randomised, active-controlled trial Setting Departments of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland Date of study Not reported. Duration of study 9 months
Participants	N = 20 Mean age = 29 years **Inclusion criteria of the trial** • Hirsute women between 18 to 40 years (Ferriman-Gallwey score > 10) **Exclusion criteria of the trial** • Drugs for hirsutism < 3 months prior to study Randomised N = 20 Withdrawals/losses to follow-up • 6/20 (30%); 2/10 in GnRH-a group, 4/10 in GnRH-a + hormone replacement therapy (HRT) group • Vasomotor symptoms; 1/10 in GnRH-a group, 0/10 in GnRH-a + HRT group • Depression; 1/10 in GnRH-a group, 0/10 in GnRH-a + HRT group • Heavy uterine bleeding; 0/10 in GnRH-a group, 1/10 in GnRH-a + HRT group • Headache; 0/10 in GnRH-a group, 1/10 in GnRH-a + HRT group • Premenstrual tension; 0/10 in GnRH-a group, 2/10 in GnRH-a + HRT group Baseline data (mean (SD)) BMI: GnRH-a group 26.1 (8.3), GnRH-a + HRT group 29.4 (9.9) F-G score: GnRH-a group 17.0 (5.7), GnRH-a + HRT group 20.6 (7.4) SHBG (nmol/L): GnRH-a group 42.9 (22.0), GnRH-a + HRT group 31.8 (20.4) Testosterone (nmol/L): GnRH-a group 4.65 (2.99), GnRH-a + HRT group 3.50 (0.99) Free testosterone (pmol/L): GnRH-a group 65.6 (35.1), GnRH-a + HRT group 56.9 (22.2) Androstenedione (nmol/L): GnRH-a group 12.4 (5.0), GnRH-a + HRT group 12.4 (3.9) DHEAS (μmol/L): GnRH-a group 9.6 (4.3), GnRH-a group + HRT 10.0 (5.3)
Interventions	**Intervention** • Goserelin implant every 28 days for 9 months (10) **Comparator** • Goserelin implant every 28 days for 9 months + after first 3 months also oestrogen-progestin replacement for the last 6 months (10)
Outcomes	Assessments (10): baseline and each month until end of study **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey scores * 2. FSH, LH, SHBG, total testosterone, free testosterone, androstenedione, DHEAS, prolactin * * Denotes outcomes prespecified for this review

Notes	Participants were not randomised for first 3 months of the study and all received GnRH-a, only randomised for the last 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 448): "...were randomized (by use of a sealed envelope)..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 448): "...were randomized (by use of a sealed envelope)..." Comment: the report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	6/20 (30%); 2/10 in GnRH-a group, 4/10 in GnRH-a + hormone replacement therapy (HRT), reasons reported Per-protocol analysis Comment: the high drop-out rate with per-protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias

Other bias	Unclear risk	Quote (page 447): "This work was supported by grants from the Finnish Academy of Science and Zeneca Pharmaceuticals (Helsinki, Finland)." Comment: a potential risk of bias cannot be excluded

Unfer 2000

Methods	Randomised, active-controlled trial Setting Policlinico Monteluce, University of Perugia, Perugia, Italy Date of study Not reported. Duration of intervention 18 months
Participants	N = 40 Mean age = not reported **Inclusion criteria of the trial** • Hirsute women with PCOS **Exclusion criteria of the trial** • Nothing reported Randomised N = 40 Withdrawals/losses to follow-up • Not reported Baseline data Nothing reported
Interventions	**Intervention** • Ethinyl estradiol 0.02 mg/day for 3 weeks + the first 10 days cyproterone acetate 12.5 mg/day and then 7 pause days for 18 months (24) **Comparator** • Flutamide 250 mg/day for 18 months (16)
Outcomes	Assessments: baseline and at least end of study **Outcomes of the trial** (as reported) 1. Hirsutism score * 2. Hormone levels * 3. Multi-screen blood chemistry * Denotes outcomes prespecified for this review
Notes	Abstract to conference proceedings. Limited data provided, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Unfer 2000 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 36): "randomized" and "...assigned randomly..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

van Vloten 2002

Methods	Randomised, active-controlled trial Setting Multi-centre (6) in the Netherlands and Germany Date of study Not reported. Duration of intervention 9 months
Participants	N = 128 Mean age = 23 years **Inclusion criteria of the trial** • 16 to 35 years • Mild to moderate acne and who had minor occurrence of seborrhoea and/or hair growth on the upper lip, chin, and chest

	Exclusion criteria of the trial • Pregnancy and lactation • Contraindication to OCP • Malignancy • Vascular and metabolic diseases • Obesity (> 20% normal weight) • Pap smear > CII • Genital infection • Use of parenteral depot of OCP < 6 months prior to study entry • Presence of large nodes, cysts, fistular comedos, abscessing fistular ducts • Previous unsuccessful treatment with antiandrogenic hormone preparations for at least 3 months • Treatment with isotretinoin < 12 months Randomised N = 128 Withdrawals/losses to follow-up • 22/128 (17%); 14/82 in EE/DRSP group, 5/43 in EE/CPA group, 3/3 unclear from which group • Withdrawal of consent; 4/82 in EE/DRSP group • Protocol violation; 2/82 in EE/DRSP group • Failure to attend to the clinic; 2/82 in EE/DRSP group • Medication not taken; 1/82 in EE/DRSP group • Adverse events; 4/43 in EE/CPA group • Lost to follow-up; 1/41 in EE/CPA group Baseline data (number (%)) Facial acne: EE/DRSP group 82 (100), EE/CPA group 43 (100) Seborrhoea: EE/DRSP group 64 (78), EE/CPA group 32 (74.4) Hirsutism location upper lip: EE/DRSP group 13 (15.9), EE/CPA group 6 (14.0) Hirsutism location chin: EE/DRSP group 3 (3.7), EE/CPA group 3 (7.0) Hirsutism location chest: EE/DRSP group 1 (1.2), EE/CPA group 3 (7.0)
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 9 months (82) **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 9 months (43)
Outcomes	Assessments (5): baseline, month 1, 3, 6, and 13 **Outcomes of the trial** (as reported) 1. Acne lesion count (comedones, papules, pustules and nodules) * 2. Sebum production; Sebumeter 3. Ferriman-Gallwey score * 4. Total testosterone, free testosterone, androstenedione, DHEAS, SHBG, FSH, LH * 5. Haematological and chemistry screening 6. Self evaluation * 7. Adverse events

	* * Denotes outcomes prespecified for this review
Notes	Only few women were hirsute, no separate data for hirsute women, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 4): "...were randomized to receive in a 2:1 ratio..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 4): "...one tablet of the allocated study preparation and one tablet identical to the study preparation were taken..." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by participants and investigators. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	22/128 (17%); 14/82 in EE/DSRP group, 5/43 in EE/CPA group, 3/3 unclear from which group. Both intention-to-treat analysis and per-protocol analysis. Inconsistent reporting of data Comment: considerable drop-out rate

van Vloten 2002 (*Continued*)

		combined with inconsistent reporting of data; we judged this as at a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	2 of the authors were employed by Schering, the manufacturer of the OCPs Comment: a potential risk of bias cannot be excluded

Vegetti 1996

Methods	Randomised, open, active-controlled trial Setting Multi-centre (4), in Italy Date of study Not reported. Duration of intervention 48 weeks with follow-up at 24 weeks
Participants	N = 56 Mean age = 24 years **Inclusion criteria of the trial** • Hirsute women > 17 years with Ferriman-Gallwey score >10 • Normal biochemical and haematological values **Exclusion criteria of the trial** • OCP or hormonal medication < 2 months prior to study entry Randomised N = 56 Withdrawals/losses to follow-up • 15/56 (27%), 7/28 in OCP group, 8/28 in OCP + goserelin, reasons not reported Baseline data (mean (SD)) Hair diameter face, abdomen, midthigh (μm): OCP group 64.0 (14.6), OCP + goserelin 66.9 (8.6) Hair diameter forearm (μm): OCP group 49.1 (9.5), OCP + goserelin 48.1 (10.1) SHBG (nmol/L): OCP group 34.45 (21.45), OCP + goserelin 22.83 (14.82) DHEAS (μg/ml): OCP group 1.99 (0.73), OCP + goserelin 2.28 (0.63) Free testosterone (pg/ml): OCP group 2.35 (1.71), OCP + goserelin 2.37 (1.20) DHT (pg/ml): OCP group 0.31 (0.11), OCP + goserelin 0.23 (0.06)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) for 48 weeks (28) **Comparator** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + monthly depot of goserelin for 48 weeks (28)

Outcomes	Assessments (4): baseline, week 24, 48 and 24 weeks after end of study **Outcomes of the trial** (as reported) 1. Subjective response of hair growth and satisfaction by physician and participant; 3-point Likert scale * 2. Acne; 4-point Likert scale * 3. Estradiol, SHBG, DHEAS, free testosterone, DHT, LH, FSH * 4. Objective response (hair diameter) 5. Serum chemistry, urine analysis, complete blood count 6. Adverse events * * Denotes outcomes prespecified for this review
Notes	Inconsistent N is used for the different analyses as not always all 41 participants were available for the measurements; these are listed in the tables of the paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 261): "...using a multiple computer generated scheme...were centrally randomized..." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: central allocation, probably done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 260): "...open..." Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 260): "...open..." Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	15/56 (27%), 7/28 in OCP group, 8/28 in OCP + goserelin, reasons not reported. Per-protocol analysis Comment: the high drop-out rate with per-

		protocol analysis represents a potential high risk of bias
Selective reporting (reporting bias)	High risk	Although subjective evaluation and 'patient satisfaction' were prespecified assessments, no data are reported on these outcomes Comment: we judged this as at a high risk of bias
Other bias	Low risk	Quote (page 267): "...We thank Zeneca Spa., Italy for providing the drugs..." Comment: we judged this as at a low risk of bias

Venturoli 1998

Methods	Randomised, active-controlled trial Setting Institute of Reproductive Physiology and Pathology of the University of Bologna, Bologna, Italy Date of study No reported. Duration of intervention 6 months
Participants	N = 18 Mean age = 23 years **Inclusion criteria of the trial** • Hirsute women **Exclusion criteria of the trial** • Adrenal or ovarian tumour Randomised N = 18 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data Nothing reported
Interventions	**Intervention** • OCP (ethinyl estradiol 0.01 mg/day for the 1st week, 0.02 mg/day for the 2nd week, 0.01 mg/day for the 3rd week and 7 'pause' days) + cyproterone acetate 12.5 mg/day for the first 10 days of treatment for 6 months (8) **Comparator** • OCP (ethinyl estradiol 0.01 mg/day for 10 days, 0.02 mg/day for the next 11 days and 7 'pause' days) + cyproterone acetate 12.5 mg/day for the first 10 days of treatment for 6 months (10)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score

	* 2. Hair growth; IBAS image analyser * 3. FSH, LH, DHEAS, testosterone, 17OH progesterone, DHT, androstenedione, 17β estradiol, SHBG * 4. GnRH test 5. Biochemical parameters 6. Adverse events * * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 30): "...were randomized into two different regimens..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias

Venturoli 1998 (*Continued*)

Selective reporting (reporting bias)	Low risk	Although limited data have been provided, the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 33): "This work was supported in part by a grant from Ministero dell' Università e della Ricerca Scientifica e Tecnologica(funds 60%,1997) Rome, Italy" Comment: we judged this as at a low risk of bias

Venturoli 1999

Methods	Randomised, active-controlled study Setting Reproductive Medicine Unit, Institute of Obstetrics and Gynecology, University of Bologna, Bologna, Italy Date of study Not reported. Duration of intervention 12 months
Participants	N = 66 Mean age = 23 years **Inclusion criteria of the trial** • Hirsute women **Exclusion criteria of the trial** • Hormonally active adrenal gland • Ovarian tumour • Cushing's, prolactin, or thyroid disorder Randomised N = 66 Withdrawals/losses to follow-up • 9/66 (14%); 0/15 in flutamide group, 0/15 in finasteride group, 8/16 in ketoconazole group, 1/20 in EE/CPA group Baseline data (mean (SD)) BMI: 27 (2.6) 27 had PCOS, 25 idiopathic hirsutism, 14 non-classic adrenal hyperplasia
Interventions	**Intervention** • Flutamide 250 mg/day for 12 months (15) **Comparator 1** • Finasteride 5 mg/day for 12 months (15) **Comparator 2** • Ketoconazole 300 mg/day for 12 months (16) **Comparator 3**

	• OCP (ethinyl estradiol 0.01 mg/day for the 1st week, 0.02 mg/day for the 2nd week, 0.01 mg/day for the 3rd week and 7 'pause' days) + cyproterone acetate 12.5 mg/day for the first 10 days of treatment for 12 months (20)
Outcomes	Assessments (5): baseline, month 3, 6, 9, and 12 **Outcomes of the trial** (as reported) 1. Modified Ferriman-Gallwey score * 2. Hair growth; IBAS analyser * 3. Self reported evaluation; 3-point Likert scale * 4. Biochemical parameters 5. FSH, LH, prolactin, 17OH progesterone, DHEAS, DHEA, testosterone, free testosterone, DHT, androstenedione, 17β estradiol and SHBG * 6. Adverse events * *Denotes outcomes prespecified for this review
Notes	Quote (page 1304): "Fourteen hirsute patients (21%) suffered from a mild form of nonclassic adrenal hyperplasia with high 17a-hydroxyprogesterone values, as diagnosed by ACTH test". No separate data for women with PCOS and idiopathic hirsutism, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1304): "Patients were randomized into four groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9/66 (14%); 0/15 in flutamide group, 0/15 in finasteride group, 8/16 in ketoconazole group, 1/20 in EE/CPA group. Per-protocol analysis Comment: we judged this as at unclear risk of bias
Selective reporting (reporting bias)	High risk	Self reported evaluation was a prespecified outcome but not reported Comment: we judged this as at a high risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Vermeulen 1988

Methods	Randomised, double-blind, active-controlled trial Setting Department of Endocrinology, Medical Clinic, University Hospital Ghent, Belgium Date of study Not reported. Duration of intervention 6 months
Participants	N = 30 Age range 18 to 35 years **Inclusion criteria of the trial** • Acne or hirsutism **Exclusion criteria of the trial** • Smoking > 10 cigarettes/day • Alcohol > 40 ml/day • Hypertension Randomised N = 30 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) Testosterone (ng/dl): Diane 35 group 42 (5), Diane 50 group 33 (3) DHT (ng/dl): Diane 35 group 25 (3), Diane 50 group 20 (2) Androstenedione (ng/dl): Diane 35 group 213 (21), Diane 50 group 201 (33) DHEAS (ng/dl): Diane 35 group 162 (21), Diane 50 group 155 (14)
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone 2 mg) for 6 months (13)

Vermeulen 1988 (*Continued*)

	Comparator • OCP (ethinyl estradiol 50 µg + cyproterone 2 mg) for 6 months (17)
Outcomes	Assessments (7): baseline and every month until end of study **Outcomes of the trial** (as reported) 1. Total cholesterol, HDL cholesterol, HDL2 cholesterol, HDL3 cholesterol, LDL cholesterol, ApoB containing lipoproteins, triglycerides 2. Testosterone, free testosterone, DHT, 5α-androstane-3α, 17β-diol, and its glucuronide, androstenedione, DHEA and DHEAS * *Denotes outcomes prespecified for this review
Notes	Quote (page 420): "The mildly hirsute women had been treated previously successfully with high dose CPA (50-100 mg) and ethinyl estradiol (50 µg) for several months and after a washout period of at least 2 months, they entered the study, the Diane treatment being considered as a maintenance therapy for these subjects. Data from this laboratory had previously shown that within 2 months of stopping therapy any effects of the drugs on either plasma androgen levels or lipids had disappeared." Unclear how many women were hirsute, as women with acne were also included, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 420): "...randomized..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 420): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Vermeulen 1988 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 420): "...double-blind..." Comment: as outcomes are serum tests, unlikely to be influenced by potential lack of adequate blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Vexiau 1995

Methods	Randomised, active-controlled trial Setting Endocrinology and Diabetology Department, Hôpital Saint-Louis, Paris, France Date of study July 1989 until July 1990. Duration of intervention 12 months
Participants	N = 65 Mean age = 26 years **Inclusion criteria of the trial** • Persistent acne, acne associated with hirsutism, hirsutism without acne **Exclusion criteria of the trial** • Steroid therapy < 3 months prior to study entry Randomised N = 65 Withdrawals/losses to follow-up • 10/65 (15%); 6/34 in transdermal patch group, 4/31 in oral group • Ineffectiveness; 2/34 in transdermal patch group, 0/31 in oral group • Patch intolerance; 4/34 in transdermal patch group, 0/31 in oral group • Drop-out; 0/34 in transdermal patch group, 1/31 in oral group • Moved away; 0/34 in transdermal patch group, 2/31 in oral group • Morbus Pfeiffer; 0/34 in transdermal patch group, 1/31 in oral group Baseline data (mean (SEM)) BMI: transdermal patch group 23.6 (0.9), oral group 20.6 (0.5)
Interventions	**Intervention** • Cyproterone acetate 50 mg/day with 17β estradiol by transdermal patch (20/28 days) for 12 months (34)

	Comparator • Cyproterone acetate 50 mg/day with 17β estradiol valerate orally (20/28) days) for 12 months (31)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Glucose tolerance 2. Plasma lipid level parameters 3. Coagulation parameters 4. Fibrinolysis parameters 5. Angiotensinogen * Denotes outcomes prespecified for this review
Notes	Unclear how many women were hirsute; no separate data for hirsute women, and none of our outcomes are assessed, see Table 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 509): "...were constituted at random..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding reported Comment: as outcomes are serum tests, unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10/65 (15%); 6/34 in transdermal patch group, 4/31 in oral group, reasons reported. Per-protocol analysis Comment: we judged this as at an unclear risk of bias

Vexiau 1995 (*Continued*)

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Vigorito 2007

Methods	Randomised controlled trial Setting University "Federico II" of Naples, School of Medicine, Naples, Italy Date of study Not reported. Duration of study 3 months
Participants	N = 90 Mean age = 22 years **Inclusion criteria of the trial** • Overweight nonsmoking women with PCOS • PCOS according to Rotterdam Criteria PCOS 2004, hirsutism according to Ferriman-Gallwey score > 8 **Exclusion criteria of the trial** • Pregnancy • Glucose intolerance (as screened by a 2-hour oral glucose tolerance test) and diabetes • Hypothyroidism • Hyperprolactinaemia • Cushing's syndrome • Nonclassical congenital adrenal hyperplasia • Use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic or anti-obesity drugs, or other hormonal drugs < 6 months prior to study entry • Neoplastic, hepatic, respiratory, and any cardiovascular disorder or other concurrent medical illness (i.e. heart failure, lung or renal disease) Randomised N = 90 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (mean (SD)) BMI: trained group 29.3 (2.9), untrained group 29.4 (3.5) F-G score: trained group 11.9 (3.5), untrained group 12.1 (3.4) Testosterone (nmol/L): trained group 2.3 (0.7), untrained group 2.5 (0.5) Androstenedione (nmol/L): trained group 5.1 (0.7), untrained group 5.3 (0.9) DHEAS (µmol/L): trained group 4320 (465), untrained group 4290 (441) SHBG (nmol/L): trained group 27 (6.2), untrained group 29 (6.5)

Interventions	**Intervention** • Exercise training 3 times a week for 30 minutes (45) **Comparator** • No exercise (45) At study entry, general dietary and behavioural advice without a structured caloric restriction programme was given to the entire PCOS study population. All of the PCOS population was counselled to achieve a healthy balanced meal plan with regular food with a nutritional composition of 50% of calories from carbohydrate, 25% from protein, and 25% from fat. Intake of low glycaemic index foods was encouraged
Outcomes	Assessments (2): baseline and month 3 **Outcomes of the trial** (as reported) 1. LH, FSH, prolactin, estradiol, progesterone, 17OH progesterone, testosterone, androstenedione, DHEAS, SHBG * 2. Ferriman-Gallwey score, BMI, waist/hip ratio * 3. Glucose and insulin (AUCs) 4. Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, C-reactive protein 5. Diary for menses and serious events * 6. Leisure-time physical activity questionnaire * Denotes outcomes prespecified for this review
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1380): "PCOS women were randomly subdivided into two groups..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement

Vigorito 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not feasible. Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	All clinical assessments were performed by the same physician who was blinded to the patient allocation into the study protocol Comment: uncertainty about the effectiveness of blinding of outcomes assessors (healthcare providers) and the lack of blinding of the outcomes (serious events and menses) by the participants poses a high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Visnovský 2010

Methods	Randomised, active-controlled trial Setting Department of Gynecology and Obstetrics, Jessenius Faculty of Medicine, Comenius University, Martin, Slovak Republic Date of study March 2003 until April 2005. Duration of the intervention 1 year
Participants	N = 90 Mean age = 25 years **Inclusion criteria of the trial** • Women with hyperandrogenic syndrome • Infertility • Nulligravida • 2 criteria of PCOS (oligo/anovulation respectively oligo/amenorrhoea, menstrual cycle of 35 to 90 days or absence of menses more than 90 days, clinical or biochemical signs of hyperandrogenism - hirsutism and virilisation on 3 predilection places, testosterone level > 0.65 nmol/L polycystic ovaries on ultrasound) **Exclusion criteria of the trial**

	• Endocrinological disease • Contraindication for OCP • Hormonal treatments • Dysmenorrhoea Randomised N = 90 Withdrawals/losses to follow-up • No losses to follow-up Baseline data Oligomenorrhoea: 82/90 Hirsutism: 54/90 Polycystic ovaries on ultrasound: 81/90 Hyperandrogenic hormone profile: 65/90
Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 12 months (30) **Comparator 1** • OCP (ethinyl estradiol 30 µg + dienogest 2 mg) for 12 months (30) **Comparator 2** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 12 months (30)
Outcomes	Assessments (4): baseline, month 6, 12, and 18 **Outcomes of the trial** (as reported) 1. Menses * 2. Effect on clinical parameters of hyperandrogenism * 3. Ultrasound of ovaries *Denotes outcomes prespecified for this review
Notes	54/90 had hirsutism, no separate data on hirsute women, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 481): "...randomized..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient informa-

Visnovský 2010 (*Continued*)

		tion to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Wang 2012

Methods	Randomised, active-controlled trial Setting Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China Date of study Not reported. Duration of intervention 6 months
Participants	N = 110 Mean age = not reported **Inclusion criteria of the trial** • PCOS diagnosed according to Rotterdam criteria (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Not reported Randomised N = 110 Withdrawals/losses to follow-up • Not reported Baseline data Nothing reported

Wang 2012 (*Continued*)

Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (55) **Comparator** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 6 months (55) Meantime, they received 1500 mg/d metformin and lifestyle modification such as dietary and exercise
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. BMI, waist/hip ratio, score of GAGS, Ferriman-Gallwey score * 2. Biochemical profile as hormone profile, HOMA-IR, the insulin and glucose AUC by means of oral glucose tolerance tests and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, and haemoglobin A1c) * Denotes outcomes prespecified for this review
Notes	Abstract to conference proceedings. Limited data and no contact details of investigators provided, see Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page S482): "...randomly separated into two groups ..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported Comment: there was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding

Wang 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	There was insufficient information to permit a clear judgement of the risk of bias

Wolf 2007

Methods	2 randomised, double-blind, vehicle-controlled trials Setting Multi-centre (18) in the US (17) and Spain (1) Date of study Not reported. Duration of intervention 24 weeks with 8 weeks follow-up
Participants	N = 596 Age range = 18 to 83 years **Inclusion criteria of the trial** • Women of at least 16 years of age with a clinical diagnosis of facial hirsutism • An average hair density of at least 5 hairs per cm^2 on both the chin and upper lip as assessed by video image analysis • Customary frequency of hair removal of at least twice per week • Good general health • A negative serum or urine pregnancy test for women of child-bearing age • A score of at least 20 on a VAS ranging from 0 (not bothered) to 100 (extremely bothered) for the question: "How much are you bothered by your facial hair?" **Exclusion criteria of the trial** • Score < 20% on a subject's self assessment questionnaire • Laser or epilation within 2 months • Chemical depilatories within 2 weeks • Bleaching within 1 week • Plucking within 48 hours or shaving within 24 hours before the study • Medications considered to have an effect on hair growth within 6 months of the study • Facial conditions such as severe inflammatory acne • Pregnancy or nursing mothers Randomised N = 596 Withdrawals/losses to follow-up • 153/596 (26%); 100/295 in eflornithine group and 53/201 in vehicle group Baseline data No data regarding hirsutism score or hormone levels
Interventions	**Intervention** • Eflornithine HCl 13.9% cream b.i.d. for 24 weeks with 8 weeks follow-up (395) **Comparator**

	• Vehicle b.i.d. for 24 weeks with 8 weeks follow-up (201) During the study, subjects were permitted to continue their normal hair removal method; however, shaving and cutting were not permitted within 24 hours of 1st day of a scheduled study visit, plucking within 48 hours, or bleaching within 1 week of the first day of a scheduled visit
Outcomes	Assessments (7): baseline, weeks 2, 4, 8, 16, 24, and 32 **Outcomes of the trial** (as reported) 1. Physician's Global Assessment (photographic assessment); 4-point Likert scale * 2. Evaluations of acne and pseudo folliculitis barbae * 3. Adverse events * * Denotes outcomes prespecified for this review
Notes	This is the same study as Jackson 2007, but partly covering other outcomes. The number of participants completing the study are not consistent in the 2 papers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 95): "Subjects were randomized to receive..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication (quote): "Subjects were assigned treatment by a computer-generated randomization schedule restricted to ensure distribution of eflornithine 15% cream and its vehicle in a 2:1 ratio, respectively, within each investigational site." Comment: probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported After e-mail communication (quote): "Subject numbers and numbers identifying study medication containers corresponded directly." and " The second panel of the tear-off part of the label was a sealed enve-

		lope concealing the identity and lot number of the treatments. These tear-off portions were to be affixed to the subjects CRFs and opened only in the case of a medical emergency in which the investigator had determined that the information was absolutely necessary, i.e., that it would alter the subjects immediate management." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 94): "...double-blind..." Comment: the report did not provide sufficient detail about the specific measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication (quote): "Blinding of the eflornithine 15% cream and its vehicle was assured by the fact that both study medications were packaged in identically appearing 15g plastic tubes bearing three-panel, two-part double-blind labels. Labels affixed to the tubes (the only label to which subjects had access) contained no evidence of the identity of the contents... Eflornithine 15% cream and its vehicle were matching cream formulations and it was not considered possible to differentiate one treatment from the other solely by tactile or visual evaluation. The protocol for this study specified that dispensing of study medications at the investigational site was to be done by a staff member who was not responsible for conducting any of the clinical evaluations. Therefore, the chances of the investigator equating a particular level of response with what he/she considered to be a particular treatment was minimal." Comment: the report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 976): "...double-blind..." Comment: uncertainty about the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail contact (quote): see above Outcomes were investigator-assessed as well as participant-assessed (menstruation). Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: we judged this as at a low risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	153/596 (26%); 100/395 in eflornithine group and 53/201 in vehicle group. Per-protocol analysis Comment: high drop-out rate with per-protocol analysis represents a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	High risk	Quote (page 97): "These studies were funded by the partnership of Bristol-Myers Squibb, Princeton, NJ and The Gillette Company, Needham, MA. Eflornithine HCl 13.9% cream is marketed as Vaniqa® (SkinMedica Inc., Carlsbad, CA and Shire Pharmaceuticals Group PLC, UK)" Comment: a potential risk of bias cannot be excluded

Wong 1995

Methods	Randomised, active-controlled trial Setting Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Southern California School of Medicine, Los Angeles, California, US Date of study Not reported. Duration of intervention 6 months
Participants	N = 14 Mean age = 31 years **Inclusion criteria of the trial** • Women 15 to 40 years with moderate to severe hirsutism • Ferriman-Gallwey score > 12 **Exclusion criteria of the trial** • Evidence of virilisation, pelvic mass, or elevated 17-hydroxyprogesterone levels Randomised N = 14 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SEM)) F-G score: spironolactone group 19 (2), finasteride group 19 (2) Testosterone (pmol/L): spironolactone group 1838 (347), finasteride group 1422 (173) DHT (pmol/L): spironolactone group 544.1 (79.2), finasteride group 509.6 (58.5) Androstenedione (pmol/L): spironolactone group 9777 (1,466), finasteride group 7926 (873) DHEAS (nmol/L): spironolactone group 8163 (2449), finasteride group 8707 (1905)
Interventions	**Intervention** • Spironolactone 100 mg daily for 6 months (5) **Comparator** • Finasteride 5 mg daily for 6 months (9) All were fully informed of the potential risk should they have become pregnant with a male fetus during the trial and were either using or were placed on non hormonal forms of contraception
Outcomes	Assessments (3): baseline, month 3 and 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. Total testosterone, DHT, androstenedione, DHEAS * 3. Hair analysis; optic micrometer * 4. Self reported assessment; 6-point Likert scale * * Denotes outcomes prespecified for this review
Notes	-

Wong 1995 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 233): "...were randomly assigned in a 1:2 ratio..." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	The study appears to be free of other forms of bias

Zheng 2005

Methods	Randomised, active-controlled trial Setting Research laboratory of Reproductive Endocrinology, First Hospital of Xi'an Jiaotong University, Xi'an, China Date of study Not reported. Duration of intervention 6 months
Participants	N = 90 Mean age = 29 years **Inclusion criteria of the trial** • PCOS based on the presence of oligomenorrhoea or amenorrhoea, hyperandrogenism (testosterone levels > 2.8 nmol/L, serum LH/FSH ratio ≥ 2, and ultrasound evidence of polycystic ovaries (presence ≥ 10 cysts, 2 mm to 8 mm in diameter) • Clomiphene citrate resistant **Exclusion criteria of the trial** • Not reported Randomised N = 90 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (mean (SD)) BMI: metformin group 25.30 (3.64), rosiglitazone group 26.67 (3.67) F-G score: metformin group 9.35 (1.41), rosiglitazone group 9.62 (1.58) Testosterone (nmol/L): metformin group 2.82 (1.51), rosiglitazone group 3.09 (0.73)
Interventions	**Intervention** • Metformin 500 mg 3 times a day + clomiphene citrate 50 to 100 mg/day during day 5 to 9 of the menstrual cycle for 6 months (50) **Comparator** • Rosiglitazone 4 mg once a day + clomiphene citrate 50 to 100 mg/day during day 5 to 9 of the menstrual cycle for 6 months (40)
Outcomes	Assessments (7): baseline, month 1, 2, 3, 4, 5, and 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. BMI, weight * 3. Ultrasonography for ovaries/cysts/follicles 4. LH, FSH, prolactin, estradiol, testosterone * 5. Oral glucose tolerance test, insulin release test 6. HOMA-IR * Denotes outcomes prespecified for this review
Notes	-
Risk of bias	

Zheng 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 63): "...randomized to receive. .." Comment: insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment, was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported Comment: the outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding reported Comment: the outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported Comment: we judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: we judged this as at a low risk of bias
Other bias	Low risk	Quote (page 62): "This work was supported by the Foundation of Science & Technique Investigation Project of Shaanxi Province." Comment: we judged this as at a low risk of bias

ACE: angiotensin-converting-enzyme
AUC: area under the curve
b.i.d.: twice a day
BMI: body mass index
CAH: congenital adrenal hyperplasia

CC: clomiphene citrate
CMA: chlormadinone acetate
CPA: cyproterone acetate
DHEAS: dehydroepiandrosterone sulphate
DHT: dihydrotestosterone
DQLI: Dermatology Quality of Life Index
DRSP: drospirenone
DSG: desogestrel
EE: ethinyl estradiol
FAI: Free Androgen Index
F-G: Ferriman-Gallwey score
FSH: follicle-stimulating hormone
GnRH-a: gonadotropin-releasing hormone analogue
HDL: high-density lipoprotein
HOMA-IR: Homeostasis Model Assessment Insulin Resistance index
IH: idiopathic hirsutism
im: intramuscular
iv: intravenous
IVF: in vitro fertilisation
LDL: low-density lipoprotein
LH: luteinising hormone
LHRH: luteinising hormone-releasing hormone
OCP: oral contraceptive pill
OGTT: oral glucose tolerance test
PCOS: polycystic ovary syndrome
PI: principal investigator
QUICKI: Quantitative Insulin Sensitivity Check Index
sc: subcutaneous
SD: standard deviation
SEM: standard error of the mean
SHBG: sex hormone-binding globulin
TSH: thyroid-stimulating hormone
UTND: ultrasound-guided transvaginal needle ovarian drilling
VAS: visual analogue scale
VLDL: very low-density lipoprotein

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acién 1997	Full text confirms: CCT
Anderson 1977	Full text confirms: CCT
Ansarin 2007	Abstract (English) confirms: CCT
Avnstorp 1982	Translated from Swedish, full text confirms case series
Baranowska 1983	Translated from Polish, full text confirms CCT see Acknowledgements

(*Continued*)

Barrett-Connor 1999	Interventions not relevant for this review
Barth 1989	Full text confirms: CCT
Batukan 2006	Partial report (only one treatment arm); full data set in Batukan 2007
Bazex 1982	Translated from French, full text confirms case series
Benjamin 1971	Full text confirms: CCT
Bridger 2006	Full text confirms: participants were not hirsute
Buckshee 1986	Full text confirms: CCT
Carmina 1997	Full text confirms: CCT
Castel-Branco 1998	Full text confirms: CCT
Castello 1991	Full text confirms: CCT
Codner 2009	Full text: hirsutism was not a prerequisite inclusion criterion
Cremoncini 1976	Full text confirms: CCT
Cullberg 1985	Full text confirms: CCT
Cunliffe 1973	Full text confirms: within-patient controlled study (CCT)
Dahlgren 1998	Full text confirms: CCT
Dennerstein 1984	Full text confirms: CCT
Devoto 2000	Full text confirms: CCT
Devoto 2004	Full text confirms: CCT
Dikensoy 2009	Full text confirms: CCT
Erdmann 1994	Translated from German, full text confirms CCT
Erenus 1995	Full text, letter to the editor commenting on Cusan 1994
Escobar-Morreale 1998	Full text confirms: CCT
Falsetti 1997	Full text confirms quasi-randomised (CCT)
Falsetti 1997B	Full text confirms quasi-randomised (CCT)

(*Continued*)

Fruzzetti 1993	Full text confirms quasi-randomised (CCT)
Givens 1976	Full text confirms: CCT
Gomez 1987	Full text, letter to the editor confirms CCT
Gregoriou 2000	Full text confirms: CCT
Grigoriou 1996	Full text confirms quasi-randomised (CCT)
Grund 1975	Translated from German, full text confirms CCT
Gupta 1978	Full text confirms: CCT
Guzick 1994	Full text: not on interventions for hirsutism
Gökmen 1996	The investigators describe a method used to generate the allocation sequence that does not provide comparable groups (quasi-randomised)
Hahn 2004	Full text confirms: CCT
Inal 2005	Full text confirms quasi-randomised (CCT)
Jasonni 1991	Full text confirms: case series
Karakurt 2008	Full text confirms quasi-randomised (CCT)
Kazerooni 2010	Full text confirms quasi-randomised (CCT)
Keletimur 1998	Full text confirms quasi-randomised (CCT)
Keletimur 2004	Full text confirms quasi-randomised (CCT)
Knopp 2001	Full text, not in hirsute women
Lachnit-Fixson 1979	Full text confirms: literature review, non-RCT
Landman 2001	Full text, letter to the editor commenting on Azziz 2001
Le Donne 2012	After e-mail contact with trialist, confirmed as quasi-randomised (CCT). See Table 4
Lee 2000	Full text, summary of related Cochrane Review (Brown 2009), non-RCT
Lobo 1985	Full text confirms: CCT
Lunde 1987	Full text confirms: CCT

(*Continued*)

Madani 2012	After e-mail contact with trialist, confirmed as quasi-randomised (CCT). See Table 4
Manieri 1997	Full text confirms: CCT
Medical Letter 2000	Full text: a short summary on eflornithine hydrochloride cream 13.9%, following its approval by FDA
Mowbray 1959	Full text confirms: case series
Müderris 1997	Full text confirms quasi-randomised (CCT)
Nielsen 1985	Translated from Danish, full text confirms CCT
Paggi 1981	Translated from Italian, full text confirms case series
Pai 1982	Full text confirms: case series, with only one woman with hirsutism
Pedersen 1985	Translated from Danish, full text confirms case series
Peereboom-Wynia 1985	Full text confirms: CCT
Pugeat 1991	Translated from French, full text confirms CCT
Rubens 1985	Full text confirms: CCT
Sahin 2001	Full text confirms quasi-randomised (CCT)
Sert 2003	Full text and e-mail contact with trialist confirms: quasi-randomised (CCT). See Table 4
Siegberg 1987	Full text confirms: CCT
Taner 2002	Full text confirms quasi-randomised (CCT)
Thomas 1985	Full text confirms: CCT
Tolino 1996	Full text confirms: case series
Unluhizarci 2009	Full text confirms quasi-randomised (CCT)
Unlühizarci 2002	Full text confirms quasi-randomised (CCT)
van Wayjen 1976	Translated from Dutch, full text confirms review
Vicente 2009	Full text confirms that although these women have an excess of terminal hairs in androgen-dependent areas, they did not meet the Ferriman-Gallwey criteria for hirsutism (mean score of 4)
Wagner 1993	Full text confirms: literature review

(*Continued*)

Weiss 2007	Translated from German, full text confirms non-RCT, summary of Batukan 2007
Wild 1991	Full text confirms: CCT, selected on the basis of contraceptive need and allocated according to the need
Yari 2010	Study objectives not relevant for this systematic review
Yilmaz 2005	Full text confirms quasi-randomised (CCT)
Yücelten 1999	Full text confirms: CCT

CCT controlled clinical trial (quasi-randomised)
FDA: (US) Food and Drug Administration

Characteristics of studies awaiting assessment *[ordered by study ID]*

Akha 2014

Methods	Randomised, double-blind, placebo-controlled trial Setting Several departments, Mazandaran University of Medical Sciences, Sari, Iran Date of study 2009-2011. Duration of intervention 24 weeks
Participants	N = 44 Mean age = 26 years **Inclusion criteria of the trial** • 15 to 45 years • Mild to moderate hirsutism limited to the face **Exclusion criteria of the trial** • Increased serum androgen level • Irregular menstrual cycle • Severe hirsutism • History of using spironolactone, cyproterone acetate, cyproterone compound, corticosteroids, medroxyprogesterone acetate, contraceptive pills • Also, pregnant and lactating women • Use of laser therapy for hair depilation during the previous 6 months Randomised N = 44 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data Degree of hirsutism: fennel group mild 2, moderate 20, control group mild 8, moderate 12
Interventions	**Intervention** • Fennel gel 3% for 24 weeks (22) **Comparator**

	• Placebo gel for 24 weeks (22)
Outcomes	Assessments (2): baseline, week 24 **Outcomes of the trial** (as reported) 1. Change in hair thickness; microscope * 2. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

Atabekoglu 2013

Methods	Randomised, active-controlled trial Setting Obstetrics and Gynecology, Ankara University, Ankara, Turkey Date of study Not reported. Duration of intervention 12 months
Participants	N = 52 Mean age not reported **Inclusion criteria of the trial** • PCOS **Exclusion criteria of the trial** • Not reported Randomised N = 52 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data Nothing reported
Interventions	**Intervention** • OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) once a day for 12 months (26) **Comparator** • OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) once a day for 12 months (26)
Outcomes	Assessments (unclear): baseline, month 12 and probably more **Outcomes of the trial** (as reported) 1. BMI, WHR * 2. Modified Ferriman-Gallwey score * 3. Changes in androgens (not specified) * *Denotes outcomes prespecified for this review

Notes	Poster abstract: Conference: International Federation of Fertility Societies 21st World Congress on Fertility and Sterility and the 69th Annual Meeting of the American Society for Reproductive Medicine, IFFS-ASRM 2013 Boston, MA United States

Chung 2014

Methods	Randomised, active-controlled, cross-over study Setting Paediatric and adolescent gynaecology clinic (PAGC) of a university-affiliated tertiary hospital, Hong Kong Date of study July 2007- July 2010. Duration of intervention 12 months
Participants	N = 76 Mean age = 17 years **Inclusion criteria of the trial** • Adolescents aged 14 to 19 with PCOS according to the Rotterdam consensus (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Current desire for fertility • Confirmed concomitant diabetes mellitus • Liver disease, or other medical conditions where MPA or Diane-35 may be contraindicated • Unable to give informed consent Randomised N = 76 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data (SD) F-G score: group 1 7.7 (6.4), group 2 7.7 (6.0)
Interventions	**Intervention** • Medroxyprogesterone acetate (MPA) 10 mg per day first 10 days of the month for 4 months followed by a wash-out period of 4 months and then Diane-35 for 4 months (38) **Comparator** • Medroxyprogesterone acetate (MPA) 10 mg per day first 10 days of the month followed by a wash-out period of 4 months and then medroxyprogesterone acetate (MPA) 10 mg per day first 10 days of the month for 4 months (38)
Outcomes	Assessments (4): baseline, month 4, 8, and 12 **Outcomes of the trial** (as reported) 1. BMI * 2. Waist to hip ratio 3. Serum testosterone, LH, FSH * 4. Acne * 5. Ferriman-Gallwey score *

	6. Chinese validated standard questionnaire 36-item Short Form Health Survey (SF-36) and a client satisfaction questionnaire * * Denotes outcomes prespecified for this review
Notes	-

Ibañez 2013

Methods	Randomised, open-label, active-controlled trial Setting Adolescent Endocrinology Unit of Sant Joan University Hospital, Barcelona, Spain Date of study 2010. Duration of intervention 6 months
Participants	N = 34 Mean age = 16 years **Inclusion criteria of the trial** • Girls with hyperinsulinaemic androgen excess • Hyperinsulinaemia, defined as fasting insulinaemia above 15 µU/ml and/or a peak insulinaemia above 150 µU/ml, and/or mean insulinaemia above 84 µU/ml on a 2-horal glucose tolerance test • Presence of both clinical and biochemical androgen excess, as defined by the following: hirsutism score > 8 (Ferriman-Gallwey), amenorrhoea (no menses for 3 months) or oligomenorrhoea (menstrual cycles > 45 days); and high circulating levels of androstenedione or testosterone in the follicular phase (days 3 to 7) or after 2 months of amenorrhoea **Exclusion criteria of the trial** • Evidence of anaemia • Thyroid dysfunction • Bleeding disorder • Cushing syndrome • Hyperprolactinaemia • Glucose intolerance; diabetes mellitus • Late-onset adrenal hyperplasia • Abnormal electrolytes • Abnormal screening of liver or kidney function • Use of medication affecting gonadal or adrenal function, or carbohydrate or lipid metabolism • Pregnancy Randomised N = 34 Withdrawals/losses to follow-up • No losses to follow-up reported Baseline data [Mean (SEM)] BMI: EE-CPA group 23.1 (0.6), PioFluMet group 23.2 (0.5) F-G score: EE-CPA group 13.5 (0.9), PioFluMet group 14.0 (0.9) Acne score: EE-CPA group 2.2 (0.2), PioFluMet group 2.3 (0.2) SHBG (nmol/L): EE-CPA group 23.0 (3), PioFluMet group 28 (3) Testosterone (ng/dl): EE-CPA group 58 (7), PioFluMet group 63 (7) Androstenedione (ng/dl): EE-CPA group 455 (32), PioFluMet group 474 (44) DHEAS (µg/dl): EE-CPA group 283 (32), PioFluMet group 287 (29)

Ibañez 2013 (*Continued*)

Interventions	**Intervention** • OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months (17) **Comparator** • Pioglitazone 7.5 mg + flutamide 62.5 mg + metformin 850 mg for 6 months (17)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. Weight, height, BMI * 2. Ferriman-Gallwey score * 3. Acne score; Leeds grading scale (O'Brien 1998) * 4. Glucose, insulin, lipid profile 5. SHBG, testosterone, androstenedione, DHEAS * 6. C-reactive protein, IGF-1, leptin, high molecular weight adiponectin, and follistatin, blood count and liver and kidney function 7. Carotid intima-media thickness 8. Body composition (dual-energy x-ray absorptiometry) and abdominal fat distribution (MRI) * Denotes outcomes prespecified for this review
Notes	Is full text report of the included Ibanez 2012 and will be addressed in next update

Lai 2014

Methods	Randomised, participant-blinded, active-controlled trial Setting Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Hampshire, United Kingdom Date of study January 2013-July 2013. Duration of intervention 6 months
Participants	N = 40 Mean age not reported **Inclusion criteria of the trial** • PCOS presenting with oligo- or amenorrhoea • 18 to 44 years **Exclusion criteria of the trial** • Not reported Randomised N = 40 Withdrawals/losses to follow-up • 11/40 (28%); 4 in standardised Chinese herbal medicine (CHM), 7 in individualised CHM • Adverse events; 2 in standardised CHM, 3 in individualised CHM • Taste; 1 in standardised CHM, 2 in individualised CHM • Pregnancy; 0 in standardised CHM, 2 in individualised CHM Baseline data

Lai 2014 (*Continued*)

	Nothing reported
Interventions	**Intervention** • Standardised Chinese herbal medicine 8 g b.i.d. for 6 months (20) **Comparator** • Individualised Chinese herbal medicine 8 g b.i.d. for 6 months for 6 months (20)
Outcomes	Assessments (8): baseline, week 2, 4, 8, 12, 16, 20, and 24 **Outcomes of the trial** (as reported) 1. Menstrual regularity * 2. BMI * 3. Waist hip ratio 4. Modified Ferriman-Gallwey score * 5. Dermatology Life Quality Index, Measure Yourself Medical Outcome Profile * 6. Liver and kidney function 7. Adverse events * *Denotes outcomes prespecified for this review
Notes	Conference: International Research Congress on Integrative Medicine and Health, IRCIMH 2014 Miami, FL United States

Martin Hernandez 1995

Methods	Randomised, active-controlled trial Setting Department of Endocrinology and Dermatology and Venereology, University Hospital "Virgen Macarena", Sevilla, Spain Date of study Not reported. Duration of intervention 6 months
Participants	N = 31 Mean age = 26 years **Inclusion criteria of the trial** • PCOS • Ferriman-Gallwey score $\geq$ 8 **Exclusion criteria of the trial** • Idiopathic hirsutism • Adrenal cause of hirsutism • Pregnancy • OCP < 6 months before study entry Randomised N = 31 Withdrawals/losses to follow-up

Martin Hernandez 1995 (*Continued*)

	• No losses to follow-up reported Baseline data BMI: CPA group 26.3, flutamide group 25.2 Ferriman-Gallwey score: CPA group 14.1, flutamide group 14.9 Testosterone: CPA group 108.4, flutamide group 105.4
Interventions	**Intervention** • Cyproterone acetate 100 mg/day for 6 months (17) **Comparator** • Flutamide 250 mg b.i.d. for 6 months (14)
Outcomes	Assessments (2): baseline, month 6 **Outcomes of the trial** (as reported) 1. Serum testosterone, LH, FSH, prolactin, DHEAS, androstenedione * 2. Ferriman-Gallwey score * 3. Adverse events * * Denotes outcomes prespecified for this review
Notes	Randomisation according to age, BMI, and hormone levels. Unclear if stratified randomisation took place or that the study is quasi-randomised

Mazza 2014

Methods	Randomised, active-controlled trial Setting Endocrine Unit of University "Magna Græcia" of Catanzaro, Italy Date of study Not reported. Duration of intervention 6 months
Participants	N = 56 Mean age = 23 years **Inclusion criteria of the trial** • Overweight/obese women with PCOS • Ferriman-Gallwey score $\geq$ 8 **Exclusion criteria of the trial** • Pregnancy • Thyroid disorders • Abnormal prolactin • Late-onset non-classic congenital hyperplasia • Cushing's disease • OCP < 6 months before study entry • Antihypertensive agents, antidiabetic drugs and agents for weight loss Randomised N = 56 Withdrawals/losses to follow-up

Mazza 2014 (*Continued*)

	• 4/56 (7%); 2 in each group lost to follow-up Baseline data (SD) BMI: LSM group 31.1 (5), LSM + spironolactone group 32.8 (5.6) Ferriman-Gallwey score: LSM group 12.2 (5.1), LSM + spironolactone group 15.1 (6.2) Testosterone (ng/dl): LSM group 77.3 (25.1), LSM + spironolactone group 69.3 (15.6)
Interventions	**Intervention** • Lifestyle modification plus metformin 1700 mg/day for 6 months (28) **Comparator** • Lifestyle modification plus metformin 1700 mg/day + 25 mg spironolactone for 6 months (58)
Outcomes	Assessments (2): baseline, month 6 **Outcomes of the trial** (as reported) 1. Anthropometric parameters (height, weight, waist circumference, and BMI) * 2. Menstrual cycles * 3. Ferriman-Gallwey score * 4. Laboratory investigations included glycaemia, lipid profile, blood count, coagulation parameters, and hepatic adrenal function indexes 5. Serum testosterone, SHBG, androstenedione, DHEAS, FAI * *Denotes outcomes prespecified for this review
Notes	-

Mirfeizi 2013

Methods	Randomised, single-blind, active-controlled trial Setting Nursing and Midwifery, Islamic Azad University Karaj Branch, Karaj, Iran Date of study Not reported. Duration of intervention 12 weeks
Participants	N = 50 Mean age unreported **Inclusion criteria of the trial** • PCOS **Exclusion criteria of the trial** • Not reported Randomised N = 50 Withdrawals/losses to follow-up • Not reported Baseline data (SD) Nothing reported

Interventions	**Intervention** • Diet for 12 weeks (25) **Comparator** • Physical activity for 12 weeks (25)
Outcomes	Assessments (2): baseline, week 12 **Outcomes of the trial** (as reported) 1. Serum FSH, LH, estradiol, free testosterone, testosterone, SHBG, T3, T4, TSH, hydroxy progesterone, cholesterol * 2. BMI * 3. Ultrasound * 4. Menstrual cycles * 5. Acne * 6. Ferriman-Gallwey score * 7. Alopecia *Denotes outcomes prespecified for this review
Notes	Probably CCT

Nidhi 2013

Methods	Randomised, active-controlled trial Setting Swami Vivekananda Yoga Anusandhana Samsthana, Division of Yoga and Life Sciences, Bangalore, India Date of study Not reported. Duration of intervention 12 weeks
Participants	N = 90 Mean age = 16 years **Inclusion criteria of the trial** • 15 to 18 years with PCOS according to Rotterdam criteria (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • OCP < 6 weeks prior to study entry • Insulin-sensitising agents < 6 weeks prior to study entry • Thyroid abnormalities • Non-classic adrenal hyperplasia • Prior experience with yoga • No consent Randomised N = 90 Withdrawals/losses to follow-up • 18/90 (20%); 8 in yoga group, 10 in control group

	Baseline data (SD) Number of girls with mF-G score > 6: yoga group 15, control group 13
Interventions	**Intervention** • Yoga exercises for 12 weeks (25) **Comparator** • Physical exercises for 12 weeks (25)
Outcomes	Assessments (2): baseline, week 12 **Outcomes of the trial** (as reported) 1. Serum Anti-Müllerian hormone, FSH, LH, estradiol, free testosterone, testosterone, SHBG, T3, T4, TSH, hydroxy progesterone, cholesterol * 2. BMI * 3. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review
Notes	-

Romualdi 2013

Methods	Randomised, open-label, active-controlled trial Setting Department of Obstetrics and Gynaecology, Università Cattolica del Sacro Cuore, Roma Date of study Not reported. Duration of intervention 12 months
Participants	N = 30 Mean age = 22 years **Inclusion criteria of the trial** • 18 to 30 years with PCOS according to Rotterdam criteria (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Pregnancy • Past history of cardiovascular disease • Diabetes mellitus (or impaired glucose tolerance as determined by a standard 75 g oral glucose tolerance test) • Hypertension, significant liver or renal impairment • Other hormonal dysfunction (hypothalamic, pituitary, thyroidal or adrenal causes for the clinical signs) • Neoplasms, and unstable mental illness • The presence of a late-onset adrenal enzyme defect Randomised N = 30 Withdrawals/losses to follow-up • 4/30 (13%); 2 in each group • Reasons reported for loss to follow-up; distance and time consuming Baseline data (SD) F-G score: group 20EE + DRSP 11.62 (5.66), group 30EE + DRSP 16.42 (5.88)

	BMI: group 20EE + DRSP 22.13 (3.34), group 30EE + DRSP 22.65 (2.75)
Interventions	**Intervention** • OCP (ethinyl estradiol 20 µg + drospirenone 3 mg) for 12 months (15) **Comparator** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 12 months (15)
Outcomes	Assessments (3): baseline, month 6 and 12 **Outcomes of the trial** (as reported) 1. FSH, LH, estradiol, free testosterone, testosterone, SHBG, progesterone, 17 hydroxy progesterone, DHEAS * 2. Plasma glucose, total cholesterol, triglycerides, LDL, VLDL 3. Ferriman-Gallwey score * * Denotes outcomes prespecified for this review
Notes	-

Sangeeta 2012

Methods	Randomised, double-blind, active-controlled trial Setting Department of Obstetrics & Gynecology, Gandhi Medical College, Hyderabad, Andhra Pradesh, India Date of study Not reported. Duration of intervention 6 months
Participants	N = 100 Mean age = 22 years **Inclusion criteria of the trial** • 18 to 30 years with PCOS according to Rotterdam criteria (Rotterdam Criteria PCOS 2004) **Exclusion criteria of the trial** • Pregnancy and nursing • Significant liver impairment • Significant renal impairment • Neoplastic disease • Cardiovascular diseases • Cushing's disease • Hypothyroidism • Hyperprolactinaemia • Any drug intake like antidiabetic, oestrogen and progesterone Randomised N = 100 Withdrawals/losses to follow-up • 15/100 (15%); metformin group 7, pioglitazone group 8 • Non-compliance; metformin group 2, pioglitazone group 1 • Pregnancy; metformin group 5, pioglitazone group 7 Baseline data (SD) F-G score: metformin group 15.9 (5.89), pioglitazone group 14.32 (5.29)

Sangeeta 2012 (*Continued*)

Interventions	**Intervention** • Metformin 500 mg b.i.d. for 6 months (50) **Comparator** • Pioglitazone 15 mg once a day for 6 months (50)
Outcomes	Assessments (2): baseline and month 6 **Outcomes of the trial** (as reported) 1. Menstrual cycle irregularity * 2. Ferriman-Gallwey score * 3. CBP, ESR, liver function, renal function, lipid profile, OGTT 4. Serum testosterone, SHBG, LH/FSH * 5. Ultrasound *Denotes outcomes prespecified for this review
Notes	-

Tartagni 2014

Methods	Randomised, placebo-controlled trial Setting Department of Obstetrics and Gynecology, Hospital of Sondrio, Sondrio, Italy Date of study January 2010-November 2012. Duration of intervention 6 months
Participants	N = 28 Mean age = 17 years **Inclusion criteria of the trial** • 15 to 19 years with hirsutism **Exclusion criteria of the trial** • Glucose intolerance or diabetes • Kidney, liver thyroid dysfunction • OCPs or other drugs < 6 months prior to study entry • On diet • Pregnancy • Anaemia • Bleeding disorder • Late-onset adrenal hyperplasia • Abnormal electrolytes Randomised N = 28 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (SD) F-G score: finasteride group 8.5 (1.4), placebo group 7.8 (1.2)

Tartagni 2014 (*Continued*)

Interventions	**Intervention** • Finasteride 2.5 mg every 3 days for 6 months (14) **Comparator** • Placebo for 6 months (14)
Outcomes	Assessments (3): baseline, month 3 and month 6 **Outcomes of the trial** (as reported) 1. Ferriman-Gallwey score * 2. BMI * 3. Adverse events; semi-structured talk * 4. Serum levels of transaminases (AST; ALT), total and direct bilirubin, uric acid, creatine, triglycerides, total and HDL-cholesterol, blood glucose, and estradiol 5. FSH, LH, total testosterone, DHT, DHEAS, androstenedione, androstenediol glucuronide, SHBG * Denotes outcomes prespecified for this review
Notes	-

Tirabassi 2013

Methods	Randomised, open-label, placebo-controlled trial Setting Division of Endocrinology, Department of Clinical and Molecular Sciences, Umberto I Hospital, Polytechnic University of Marche, Ancona, Italy Date of study January 2010-February 2012. Duration of intervention 3 months
Participants	N = 24 Mean age = 28 years **Inclusion criteria of the trial** • Mild idiopathic hirsutism (Ferriman-Gallwey score 8 to 15) **Exclusion criteria of the trial** • Intake of exogenous androgens • PCOS • Drug intake for hirsutism < 12 months prior to study entry • Topical treatments for hirsutism • Known hypersensitivity to components for topical treatment • Pregnancy or breast feeding • Chronic systemic disease Randomised N = 24 Withdrawals/losses to follow-up • No losses to follow-up Baseline data (SD)

Interventions	**Intervention** • Oil spray containing lavender and tea tree oil b.i.d. for 3 months (12) **Comparator** • Placebo oil spray b.i.d. for 3 months (12)
Outcomes	Assessments (2): baseline and month 3 **Outcomes of the trial** (as reported) 1. Reduction hair diameter * 2. Blood count, glycaemia, lipid profile, kidney and liver function tests, electrophoretic protidogram, total proteins; hormonal tests included TSH, LH, FSH, estradiol, progesterone, 17-hydroxyprogesterone, total testosterone, free testosterone, SHBG, DHEAS, androstenedione, prolactin, fasting insulin * 3. Ferriman-Gallwey score * 4. Adverse events * *Denotes outcomes prespecified for this review
Notes	-

ALT: alanine aminotransferase
AST: aspartate aminotransferase
b.i.d.: twice a day
BMI: body mass index
CBP: complete blood picture
CCT: controlled clinical trial
CHM: Chinese herbal medicine
CPA: cyproterone acetate
DHEAS: dehydroepiandrosterone sulphate
DHT: dihydrotestosterone
DRSP: drospirenone
EE: ethinyl estradiol
ESR: erythrocyte sedimentation rate
FAI: Free Androgen Index
F-G score: Ferriman-Gallwey score
FSH: follicle-stimulating hormone
HDL: high-density lipoprotein
LDL: low-density lipoprotein
LH: luteinising hormone
LSM: lifestyle modification
MRI: magnetic resonance imaging
MPA: medroxyprogesterone acetate
OCP: oral contraceptive pill
OGTT: oral glucose tolerance test
PCOS: polycystic ovary syndrome
SD: standard deviation
SHBG: sex hormone-binding globulin

TSH: Thyroid-stimulating hormone
VLDL: very low-density lipoprotein
WHR: waist hip ratio

Characteristics of ongoing studies *[ordered by study ID]*

IRCT201104251760N13

Trial name or title	Comparison of combined oral contraceptive Yasmin and cyproteron compound on hirsutism and androgens in women with a polycystic ovary syndrome
Methods	Randomised, double-blind, active-controlled trial in Iran
Participants	**Inclusion criteria** • 18 to 28 year-old nonsmoker women with polycystic ovary syndrome and hirsutism taking contraceptive necessities **Exclusion criteria** • Hyper-prolactinaemia • Hypothyroidism; diabetes • Doing regular intense exercise • Taking diet or herbal treatment • Non-steroidal anti-inflammatory drugs, diuretics, or hormone therapy during last 3 months
Interventions	**Intervention** • OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) for 4 months **Comparator** • OCP (ethinyl estradiol 35 µg + cyproterone acetate mg) for 4 months
Outcomes	**Primary outcomes** 1. Back to spontaneous menstrual periods **Secondary outcomes** 1. Adverse events
Starting date	20 February 2012
Contact information	Dr. Molod Aghajani-delavar moloodaghajani@yahoo.com
Notes	Website accessed 14 June 2014

IRCT2013072214106N1

Trial name or title	Studying and preparing semi-solid formulations of finasteride and clinical evaluation of optimal form in the treatment of hirsutism
Methods	Randomised, placebo-controlled trial in Iran
Participants	**Inclusion criteria** • Women after puberty that have hirsutism based on the Ferriman-Gallwey scoring system **Exclusion criteria**

IRCT2013072214106N1 (*Continued*)

	• The patient uses any other drugs • History of other disease with an appearance like hirsutism • The patient is less likely to continue participating in this study
Interventions	**Intervention** • Finasteride 0.25% gel b.i.d. for 6 months **Comparator** • Placebo gel b.i.d. for 6 months
Outcomes	**Outcomes** 1. Severity of hirsutism 2. Acne
Starting date	23 August 2013
Contact information	Dr. Ali Ebrahimi, aebrahimi@kums.ac.ir
Notes	Website accessed 14 June 2014

ISRCTN01915371

Trial name or title	Weight loss in obese women with polycystic ovary syndrome (PCOS)
Methods	Randomised controlled trial in the UK
Participants	**Inclusion criteria** • Women after puberty that have hirsutism based on the Ferriman-Gallwey scoring system • Obese women body mass index (BMI) > 30 kg/m². Aged between 20 and 40 years old who wish to conceive and have polycystic ovary syndrome (PCOS) as defined by the Rotterdam criteria (2003) **Exclusion criteria** • Previously diagnosed diabetics (both types 1 and 2) • History of renal disorder, hepatic disease, thyroid disease or cancer • Eating disorders • Weight altering medication • Weight loss > 2% in the last 3 months • Major cardiovascular or cerebrovascular event in the last 6 months • Pregnancy or lactation • Miscarriage in the last 3 months • Following contraception methods • Cardiac dysrhythmia • Porphyria (disorder of certain enzymes in the haem biosynthetic pathway) • Thrombosis • Total lactose intolerance • Convulsions, seizures, epilepsy • Major depressive episodes, psychotic episodes, schizophrenia • Serious illness, injury or trauma/surgery in the last 3 months or due to undergo surgery

ISRCTN01915371 (*Continued*)

Interventions	**Intervention** • 600 calorie deficit diet (CDD) for 6 months **Comparator** • Nutritionally balanced, commercial, very low calorie diet (VLCD) (LighterLife)
Outcomes	**Primary outcomes** 1. Weight loss will be measured with subjects wearing light clothing and no shoes, on a calibrated digital scale (Tanita Body Composition Analyzer, type BC 410 MA III) 2. Ovulation-A calendar will be provided for the patients to keep track of their menses for the 12 month duration of the study **Secondary outcomes** 1. Changes in hirsutism evaluated using the Ferriman-Gallwey questionnaire 2. Changes in quality of life evaluated using the Obesity-Related Well-Being (ORWELL 97) questionnaire 3. Changes in activity levels: a questionnaire adapted from the Framingham study will be administered to the patients 4. Changes in body composition: to ensure accuracy it will be determined by both air-displacement method (Bod Pod, Life Measurement Inc, USA) and whole body impedance analysis (Body Composition Analyzer BC-418MA, Tanita Corporation of America Inc., USA 5. Changes in androgen levels - blood samples will be drawn and analysed for levels of testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS), 17-alpha-hydroxyprogesterone (17-OHP) 6. Changes in lipid profile - blood samples will be drawn and analysed for levels of low-density lipoprotein (LDL), high-density lipoprotein level (HDL), total cholesterol levels and triglycerides 7. Changes in ACTH, cortisol 8. Changes in glycaemia and insulin sensitivity 9. Changes in levels of prolactin, progesterone, luteinising hormone (LH), follicle-stimulating hormone (FSH) , sex hormone binding globulin (SHBG) evaluated by blood tests
Starting date	1 November 2011
Contact information	Dr Catherine Rolland c.rolland@rgu.ac.uk, beca_rolland@yahoo.ca Centre for Obesity Research and Epidemiology Robert Gordon University St. Andrew Street Aberdeen, AB25 1HG, UK
Notes	Completed, no data published yet, website last accessed 13 June 2014. Sent e-mail requesting further update. E-mail address incorrect

ISRCTN29234515

Trial name or title	Ethinyl-estradiol-levonorgestrel versus low-dose pioglitazone + spironolactone + metformin in adolescents with hyperinsulinaemic ovarian hyperandrogenism: Effects on ovulatory function, parameters of chronic inflammation, on cardiovascular risk factors and on risk factors for the development of type 2 diabetes
Methods	Open, prospective, randomised study in Spain

ISRCTN29234515 (*Continued*)

Participants	**Inclusion criteria** • Age > 14 and < 18 years • Menarche at least 2 years before • BMI < 97th percentile and > 10th percentile • Clinical and biochemical hyperandrogenism • Hyperinsulinaemia (fasting and/or after an OGTT) **Exclusion criteria** • Pregnancy or pregnancy risk • Late onset congenital adrenal hyperplasia, Cushing's syndrome, uncompensated hypothyroidism • Liver or renal dysfunction, diabetes, glucose intolerance • Treatment with oral contraceptives, antiandrogens, or insulin sensitisers over the previous 6 months • Severe bacterial infections
Interventions	**Intervention** • Pioglitazone (7.5 mg/d) + spironolactone (50 mg/d) + metformin (850 mg/d), once daily, at dinner time **Comparator** • An oral contraceptive containing ethinyl-estradiol (20 µg) + levonorgestrel (100 mg), once daily
Outcomes	**Primary outcomes** 1. Fasting insulin 2. Visceral fat 3. Hepatic fat 4. Carotid intima-media thickness **Secondary outcomes** 1. Ferriman-Gallwey score 2. Androgens 3. Lipids 4. C-reactive protein 5. High molecular weight 6. Adiponectin 7. Insulin resistance index in adipocytes 8. Ovulation 9. Breast density (DXA)
Starting date	05 October 2012
Contact information	Prof Lourdes Ibañez Hospital Sant Joan de Déu University of Barcelona Passeig de Sant Joan de Deu, 2 Esplugues de Llobregat 08950 Spain libanez@hsjdbcn.org
Notes	Website accessed 13 June 2014. Study completed; no data available. Sent e-mail requesting further update Response: the preliminary (6 month) results of this trial will be presented as poster at the Endocrine Society in Chicago on June 22; they plan to go for a first publication in the autumn

NCT00145340

Trial name or title	Pioglitazone treatment in polycystic ovary syndrome
Methods	Randomised controlled trial in Denmark
Participants	**Inclusion criteria** • Hirsute women with PCOS • Irregular menses, i.e. cycle length of > 36 days • Premenopausal increased fasting insulin > 50 pmol/l • Increased free testosterone > 0.035 nmol/l **Exclusion criteria** • Age: < 18 years • Contraceptive pill within the past 3 months • Postmenopausal (increased FSH) • Known diabetes mellitus, endocrine disease or other disease requiring treatment • Drug use • Pregnancy • Planned pregnancy during the treatment period • Increased liver parameters
Interventions	**Intervention** • Pioglitazone 30 mg per day **Comparator** • Placebo
Outcomes	**Primary outcome** Glucose infusion rate (M value) below euglycaemic hyperinsulinaemic clamp (comparing baseline with 4 months)
Starting date	September 2002
Contact information	Dorte Glintborg, MD, PhD Tel: +45 6541 1769 dorte.glintborg@dadlnet.dk
Notes	Completed, no data published yet, website accessed 13 June 2014. Sent e-mail requesting further update

NCT00152048

Trial name or title	A 24 week randomised double blind placebo controlled study to evaluate the atrophogenic potential of eflornithine in the treatment of women with excessive facial hair
Methods	Randomised, controlled, double-blind trial
Participants	**Inclusion criteria** • Female subjects with clinical diagnosis of facial hirsutism/excessive facial hair • Women of childbearing potential must agree to use an effective form of birth control for the duration of the study • Skin type I-IV • Customary frequency of removal of facial hair 2 or more times per week

NCT00152048 (*Continued*)

	Exclusion criteria • Pregnant or lactating women • Severe inflammatory acne or presence of significant scarring on the face • History of skin malignancy • Connective tissue disorders
Interventions	**Intervention** • Eflornithine hydrochloride cream for 24 weeks **Comparator** • Placebo cream for 24 weeks
Outcomes	**Primary outcome** 1. Change in facial skin thickness measured by ultrasound at 24 weeks **Secondary outcomes** 1. Skin biopsies 2. Histology and histochemistry in the dermis 3. Physician Global Assessment 4. Subject Self-Assessment Questionnaire
Starting date	November 2004
Contact information	Shire Development LLC. Contact e-mail Professor Jean-Paul Ortonne: ortonne@unice.fr
Notes	Completed, no data published yet, website accessed 13 June 2014. Sent e-mail requesting further update

NCT00451568

Trial name or title	Metformin and oral contraceptives in PCOS
Methods	Randomised controlled open trial in Denmark
Participants	**Inclusion criteria** • Irregular menses or anovulatory cycles • High free testosterone > 0.035 nmol/l or hirsutism • PCO in vaginal US Criteria 1 and 2 OR 2 and 3 **Exclusion criteria** • Age > 18 years • Postmenopausal • Diagnosis diabetes mellitus • Use of medicine known to affect hormones measured in the project • Pregnancy or planned pregnancy during study period • Non-Caucasian • Previous thromboembolic disease • Heavy smoker > 35 years and BMI > 35 kg/m²
Interventions	**Intervention** • Metformin **Comparator**

NCT00451568 (*Continued*)

	• Yasmin (OAC)
Outcomes	**Primary outcome** 1. Changes in fasting insulin and area under the curve for insulin (2 hours) **Secondary outcomes** 1. Changes in BMI, WHR, LH, FSH, total and free testosterone, fasting blood glucose, fasting C-peptide, urine-cortisol secretion, body composition, number of hypoglycaemic cases, AUC for insulin, glucose and C-peptide during OGTT (2 and 5 hours)
Starting date	March 2007, estimated completion date April 2010, no further updates posted since start
Contact information	Dorte Glintborg, MD, PhD Tel: +45 6541 1769 dorte.glintborg@dadlnet.dk
Notes	Website accessed 13 June 2014. Sent e-mail requesting further update

NCT00744510

Trial name or title	Reflexology's effect on polycystic ovary syndrome (PCOS) (REPOS)
Methods	Randomised, controlled, double-blind trial in the UK
Participants	**Inclusion criteria** • Women with PCOS **Exclusion criteria** • Use of complimentary therapies within 6/12 prior to recruitment • BMI > 35 • Taken combined oral contraceptives, metformin, or cyclical progestogens within 3/12 prior to recruitment
Interventions	**Intervention** • Reflexology **Comparator** • No treatment
Outcomes	**Primary outcome** 1. To identify the most appropriate primary outcome measure for the ensuing RCT **Secondary outcomes** 1. Attainment of normal menstrual cycle length (i.e. 21 to 35 days) 2. Hormonal imbalances and irregular menses (commonly regarded at 6 cycles per annum or less) 3. Weight, body mass index (BMI), hirsutism, thinning hair 4. Fasting insulin and blood sugar levels 5. Quality of life
Starting date	December 2012
Contact information	Dawn-Marie Walker, dawn-marie.walker@nottingham.ac.uk

NCT00744510 (*Continued*)

Notes	Website accessed 13 June 2014; this study is not yet open for participant recruitment. E-mail sent requesting update

NCT00746148

Trial name or title	Reflexology's effect on polycystic ovary syndrome: A Pilot Study (REPOS)
Methods	Randomised controlled double-blind trial in the UK
Participants	**Inclusion criteria** • Women with PCOS **Exclusion criteria** • Use of complimentary therapies within 6/12 prior to recruitment • BMI > 35 • Taken combined oral contraceptives, metformin, or cyclical progestogens within 3/12 prior to recruitment
Interventions	**Intervention** • Reflexology, 10 weekly sessions of 45 minutes each **Comparator** • No treatment
Outcomes	**Primary outcome** 1. To identify the most appropriate primary outcome measure for the ensuing RCT **Secondary outcomes** 1. Attainment of normal menstrual cycle length (i.e. 21 to 35 days) 2. Hormonal imbalances and irregular menses (commonly regarded at 6 cycles per annum or less) 3. Weight, body mass index (BMI), hirsutism, thinning hair 4. Fasting insulin and blood sugar levels 5. Quality of life
Starting date	December 2012
Contact information	Dawn-Marie Walker, dawn-marie.walker@nottingham.ac.uk
Notes	Website accessed 13 June 2014, this study is not yet open for participant recruitment. E-mail sent requesting update. "Thanks for your email. I'm afraid this trial never begun, as I am still trying to get funding for it."

NCT01051024

Trial name or title	Diamel in the treatment of polycystic ovary syndrome
Methods	Randomised, controlled, double-blind trial in Cuba
Participants	18 to 40 years **Inclusion criteria** • 2 of the following criteria: oligo or anovulation polycystic ovary diagnosed by ultrasound technique;

NCT01051024 (*Continued*)

	clinical signs of hyperandrogenism • Signed informed consent **Exclusion criteria** • Personal history of other causes of hyperandrogenism: hyperprolactinaemia, suprarenal tumours, ovary tumours, suprarenal hyperplasia, hypercortisolism • Patients under other experimental treatment • Treatment with ovulation inducers and/or insulin sensitisers within 60 days before treatment • Treatment with vitamins within 7 days before treatment • Treatment with dietary supplements within 60 days before treatment • Non-compensated intercurrent diseases: diabetes mellitus, thyroid disease, hypertension
Interventions	**Intervention** • Dietary supplement: Diamel **Comparator** • Dietary supplement: placebo
Outcomes	**Primary outcomes** Normalisation of blood concentrations of 1. androgens at week 24 2. prolactin at week 24 3. oestrogens at week 24 4. FSH at week 24 5. LH at week 24 **Secondary outcomes** 1. Regularisation of the menstrual cycle at week 24 2. Reappearance of ovulatory cycles at week 24 3. Normalisation of blood concentrations of insulin at week 24 4. Normalisation of blood concentrations of cholesterol at week 24 5. Normalisation of blood concentrations of triglycerides at week 24 6. Normalisation of blood concentrations of glucose at week 24 7. Improvement of clinical signs associated with polycystic ovary syndrome: acne, hirsutism, abdominal obesity, and blood pressure at week 24
Starting date	November 2009
Contact information	Mercedes Hernandez, MD, Ramón González Coro Gynecologic and Obstetric Hospital Havana City, Havana, Cuba, 10400
Notes	Website accessed 13 June 2014, this study has been completed, no results posted. No other information or contact details

NCT01396369

Trial name or title	Impact of flaxseed lignan (Brevail) on polycystic ovarian syndrome
Methods	Randomised, controlled, open-label trial in the US

NCT01396369 (*Continued*)

Participants	**Inclusion criteria** • 18 to 40 years • Diagnosis of PCOS by menstrual irregularity (fewer than 9 menses annually/interval over 40 days), Ferriman-Gallwey score > 8, and/or hyperandrogenaemia defined as total testosterone > 80 ng/dl or bioavailable testosterone > 8.4 ng/dl • Mentally competent **Exclusion criteria** • Use of oral contraceptives, spironolactone, or insulin-sensitising agents within the past 2 months • Long-term or chronic use of oral antibiotics • Hysterectomy • FSH > 15 • Pregnancy/lactation • Consumption of flaxseed within the last month • Diagnosis of thyroid disease, nonclassical adrenal hyperplasia, and hyperprolactinaemia • Use of any dietary fibre supplements, which are newly started (within the past 6 months) and agreement not to use any new fibre supplements during the study period
Interventions	**Intervention** • OCP **Comparator** • OCP + Brevail
Outcomes	**Primary outcomes** 1. Changes of testosterone levels and hirsutism **Secondary outcomes** 1. Lipid profile and oestrogen levels
Starting date	January 2011
Contact information	Sam Kim skim2@kumc.edu
Notes	Website accessed 13 June 2014. This study is currently recruiting participants

NCT01555190

Trial name or title	Combination therapy with myo-inositol and folic acid versus myo-inositol alone: Effects of six months treatment on clinical, endocrine and metabolic features in obese women with polycystic ovary syndrome
Methods	Randomised, controlled, open-label trial in Italy
Participants	**Inclusion criteria** • Women with PCOS diagnosed in accordance with Rotterdam Consensus Conference Criteria 2003 • BMI > 25 kg/m² • Age 18 to 35 years **Exclusion criteria** • Pregnancy • Significant liver or renal impairment • Other hormonal dysfunctions (hypothalamic, pituitary, thyroidal, or adrenal causes for the clinical

NCT01555190 (*Continued*)

	signs) • Neoplasms • Unstable mental illness • Diagnosis of diabetes mellitus or impaired glucose tolerance • Use of drugs able to interfere with gluco-insulinaemic metabolism for at least 3 months prior entering the study
Interventions	**Intervention** • Myo-inositol 1500 g **Comparator** • Myo-inositol 2000 g + folic acid 200 µg
Outcomes	**Primary outcome** 1. Number of cycles in 6 months of therapy **Secondary outcomes** 1. Effects on oral glucose tolerance test 2. Effects on hormonal assay 3. Effects on lipid profile
Starting date	January 2012
Contact information	Antonio Lanzone, Catholic University of Sacred Heart Rome, Italy Maurizio Guido; maurizioguido@libero.it
Notes	Website accessed 13 June 2014. The recruitment status of this study is unknown because the information has not been verified recently. E-mail sent requesting update

NCT01626443

Trial name or title	Role of myo-inositol and D-chiro Inositol on the ovaric and metabolic functions
Methods	Randomised controlled trial in Italy
Participants	**Inclusion criteria** • PCOS • Women aged between 14 and 40 years • BMI > 28 • Hyperinsulinaemia **Exclusion criteria** • Pre-existing secondary endocrine and metabolic disorders • Pre-existing secondary adrenal disorders • Pharmacologic treatment in the last 3 months before entering the study • Pregnancy
Interventions	**Intervention** • Myo-inositol + D-chiro-inositol + folic acid **Comparator** • Folic acid

NCT01626443 (*Continued*)

Outcomes	**Primary Outcomes** 1. Menstrual cycle restoration 2. Score hirsutism (Ferriman-Gallwey classification) 3. Serum progesterone 4. Testosterone level test 5. Oral glucose tolerance test (OGTT). Evaluation of glycaemia and insulinaemia levels 6. Homeostasis Model Assessment (HOMA-index) 7. Sex hormone binding globulin (SHBG) test 8. Androstenediol level test 9. Androstenedione level test 10. Free Androgen Index (FAI) level test **Secondary Outcomes** 1. Body mass index (BMI) 2. Change from baseline in diastolic blood pressure levels 3. Change from baseline in systolic blood pressure levels 4. Number of patients with abnormal ovarian size and morphology. Ovarian ultrasound scan for the assessment of size and morphology 5. Luteinising hormone (LH) level test. Analysis of LH levels should be performed between the 7th and the 10th day of the cycle 6. Follicle-stimulating hormone (FSH) level test. Analysis of FSH levels should be performed between the 7th and the 10th day of the cycle 7. Estradiol (E2) level test. Analysis of E2 levels should be performed between the 7th and the 10th day of the cycle
Starting date	June 2012
Contact information	Elena Bonelli, University of Pisa Department of Endocrinology, Pisa, Italy; elena684@interfree.it
Notes	Website accessed 13 June 2014. The recruitment status of this study is unknown because the information has not been verified recently. E-mail sent requesting update

NCT01791647

Trial name or title	Myo-inositol versus metformin in obese women with polycystic ovary syndrome
Methods	Randomised, controlled, open-label trial in Italy
Participants	**Inclusion criteria** • Women with polycystic ovary syndrome, diagnosed in accordance with Rotterdam Consensus Conference Criteria 2003; • BMI > 25 kg/m² • Age 18 to 35 years **Exclusion criteria** • Pregnancy • Significant liver or renal impairment • Other hormonal dysfunction (hypothalamic, pituitary, thyroidal, or adrenal causes for the clinical signs) • Neoplasms

NCT01791647 (*Continued*)

	• Unstable mental illness • Diagnosis of diabetes mellitus or impaired glucose tolerance • Use of drugs able to interfere with gluco-insulinaemic metabolism for at least 3 months prior to entering the study
Interventions	**Intervention** • 1500 mg/day myo-inositol **Comparator** • 1500 mg/day of metformin
Outcomes	**Primary outcome** 1. Number of cycles **Secondary outcomes** 1. Effects of two therapies on glyco-insulinaemic metabolism 2. Area under the curve insulin post oral glucose tolerance test (μUI/ml/180 min), M value of euglycaemic hyperinsulinaemic clamp (mg/kg/min)
Starting date	June 2011
Contact information	Antonio Lanzone or Maurizio Guido 063057794
Notes	Website accessed 13 June 2014. This study is currently recruiting participants

ACTH: adrenocorticotropic hormone
AUC: area under the curve
b.i.d.: twice a day
BMI: body mass index
FSH: follicle-stimulating hormone
LH: luteinising hormone
OCP: oral contraceptive pill
OGTT: oral glucose tolerance test
PCOS: polycystic ovary syndrome
RCT: randomised controlled trial
WHR: waist hip ratio

DATA AND ANALYSES

Comparison 1. Exercise 3 times a week for 30 minutes versus no exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 2. Lifestyle modification + placebo tablets versus placebo tablets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 3. Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + drospirenone 3 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 4. Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change from baseline in Ferriman-Gallwey score	3	164	Mean Difference (IV, Random, 95% CI)	-1.84 [-3.86, 0.18]
2 Mean change from baseline in Lorenzo score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Changes in androgen levels			Other data	No numeric data

Comparison 5. Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 6. Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus other OCP (unknown)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 7. Ethinyl estradiol 35 µg + cyproterone acetate 2 mg versus ethinyl estradiol 50 µg + desogestrel 0.15 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 8. Ethinyl estradiol 30 µg + desogestrel 0.15 mg versus ethinyl estradiol 50 μg + desogestrel 0.15 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 9. Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 µg and levonorgestrel 0.15 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 10. Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 30 μg + chlormadinone acetate 2 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 11. Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg every other month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 12. Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 13. Ethinyl estradiol 30 μg + desogestrel 0.15 mg every other month versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 14. Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 μg + gestodene 75 μg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 15. Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 20 μg + drospirenone 3 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 16. Flutamide 250 mg b.i.d. versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 17. Flutamide 250 mg b.i.d. versus spironolactone 100 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 18. Spironolactone 100 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 19. Ketoconazole 400 mg per day versus ketoconazole 800 mg per day for 10 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 20. Finasteride 5 mg to 7.5 mg/day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	3	67	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.48, 2.67]
2 Mean change from baseline in Ferriman-Gallwey score	3	62	Mean Difference (IV, Random, 95% CI)	-5.73 [-6.87, -4.58]
3 Changes in androgen levels			Other data	No numeric data

Comparison 21. Finasteride 2.5 mg once a day versus finasteride 5 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 22. Finasteride 2.5 mg once a day versus finasteride 7.5 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 23. Finasteride 5 mg once a day versus finasteride 7.5 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 24. Finasteride 2.5 mg once a day versus finasteride 2.5 mg every 3 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 25. Metformin 850 mg b.i.d. versus rosiglitazone 2 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 26. Troglitazone 150 mg versus troglitazone 300 mg versus troglitazone 600 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 27. Metformin 500 mg to 1500 mg per day versus placebo for 12 to 48 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change from baseline in Ferriman-Gallwey score	7	264	Mean Difference (IV, Random, 95% CI)	-0.27 [-1.46, 0.91]
2 Changes in androgen levels			Other data	No numeric data
3 Mean change from baseline in BMI	6	252	Mean Difference (IV, Random, 95% CI)	0.56 [-0.37, 1.50]

Comparison 28. Rosiglitazone 4 mg b.i.d. versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 29. Metformin 850 mg b.i.d. versus simvastatin 20 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 30. Pioglitazone 30 mg once a day versus placebo once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 31. Lifestyle modification + metformin 850 mg b.i.d. versus metformin 850 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 32. Lifestyle modification + placebo versus metformin 850 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 33. Lifestyle modification + metformin 850 mg b.i.d. versus lifestyle modification + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 34. Lifestyle modification + metformin 850 mg b.i.d. versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 35. Metformin 2000 mg per day + lifestyle modification + OCP versus placebo + lifestyle modification + OCP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 36. OCP (ethinyl estradiol 20 µg + desogestrel 0.15 mg) + simvastatin 20 mg versus OCP (ethinyl estradiol 20 µg + desogestrel 0.15 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 37. Metformin 850 mg b.i.d. versus metformin 850 mg b.i.d. + simvastatin 20 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 38. Simvastatin 20 mg once a day versus metformin 850 mg b.i.d. + simvastatin 20 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 39. Metformin 850 mg b.i.d. + flutamide 250 mg b.i.d. versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 40. Metformin 1275 mg to 1700 mg per day + flutamide 250 mg to 500 mg per day versus flutamide 250 mg to 500 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 41. Metformin 1275 mg to 1700 mg per day + flutamide 250 mg to 500 mg per day versus metformin 1275 mg to 1700 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 42. Finasteride 5 mg once a day versus cyproterone acetate 25 mg once a day + ethinyl estradiol 20 μg 21 days of the month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 43. Flutamide 250 mg b.i.d. versus cyproterone acetate 25 mg once a day + ethinyl estradiol 20 μg 21 days of the month

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 44. Flutamide 125 mg per day + triphasic OCP versus placebo + tricyclic OCP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 45. Flutamide 250 mg per day + triphasic OCP versus placebo + tricyclic OCP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 46. Flutamide 375 mg per day + triphasic OCP versus placebo + tricyclic OCP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 47. Flutamide 125 mg per day + triphasic OCP versus flutamide 375 mg per day + triphasic OCP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 48. GnRH-A 3.75 mg im every 28 days versus GnRH-A 3.75 mg im every 28 days + oestrogen 0.625 mg and medroxyprogesterone 10 mg both on day 1 to 21

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 49. GnRH-A 3.6 mg sc every 28 days versus GnRH-A 3.6 mg sc every 28 days + estradiol valerate 2 mg days 5 to 25 + medroxyprogesterone days 16 to 25

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 50. GnRH-A 3.6 mg + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 0.35 μg + cyproterone acetate 2 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 51. GnRH-A 3.75 im every 28 days + OCP (ethinyl estradiol 35 μg + norethindrone 1 mg) versus GnRH-A 3.75 im every 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 52. GnRH-A 3.75 im every 28 days + OCP (ethinyl estradiol 35 μg + norethindrone 1 mg) versus OCP (ethinyl estradiol 35 μg + norethindrone 1 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 53. GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus GnRH-A 3.75 mg im every 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 54. GnRH-A 3.75 mg im every 28 days + flutamide 250 mg per day versus GnRH-A 3.75 mg im every 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 55. GnRH-A 3.75 mg im every 28 days + flutamide 250 mg per day versus GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 56. GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg) versus GnRH-A 3.75 mg im every 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 57. GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg) versus OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 58. GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 0.35 μg + cyproterone acetate 2 mg) versus GnRH-A 3.75 mg im every 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 59. GnRH-A 3.75 im every 28 days + conjugated oestrogen 0.625 mg + medroxyprogesterone acetate 10 mg day 1 to 12 versus OCP (ethinyl estradiol 35 µg + ethynodiol diacetate 1 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 60. OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + metformin 500 b.i.d. versus OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 61. OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + metformin 500 mg three times a day versus OCP (ethinyl estradiol 20 μg + drospirenone 3 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 62. OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) versus OCP (drospirenone 3 mg + ethinyl estradiol 20 μg) + cyproterone acetate 12.5 mg (first 10 days of pill strip)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 63. OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + metformin 500 mg three times a day versus OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + cyproterone acetate 12.5 mg (first 10 days of pill strip)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 64. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + finasteride 5 mg once a day on day 1 to 14

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 65. OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + cyproterone acetate 12.5 mg day 1 to 10 versus OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + spironolactone 100 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 66. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + cyproterone acetate 50 mg once a day on day 1 to 10 versus OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) + spironolactone 100 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 67. OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + cyproterone acetate 50 mg b.i.d. versus OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + spironolactone 100 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 68. OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + cyproterone acetate 50 mg b.i.d. versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + cyproterone acetate 50 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 69. OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + spironolactone 100 mg once a day versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + cyproterone acetate 50 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 70. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + spironolactone 100 mg once daily versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + finasteride 5 mg once daily

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 71. OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + spironolactone 100 mg versus OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + finasteride 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 72. OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + cyproterone acetate 12.5 mg day 1 to 10 versus OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + finasteride 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 73. OCP (triphasic including ethinyl estradiol and levonorgestrel) + spironolactone 100 mg once a day versus ethinyl estradiol 30 μg day on day 5 to 25 + cyproterone acetate 100 mg once a day on day 5 to 14

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 74. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + sibutramine 10 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 75. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + sibutramine 10 mg once a day versus sibutramine 10 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 76. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus pioglitazone 7.5 mg + flutamide 62.5 mg + metformin 850 mg all once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 77. Pioglitazone + transdermal contraceptive + metformin + flutamide versus placebo + transdermal contraceptive + metformin + flutamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 78. Cyproterone acetate 50 mg per day 20 days per month + ethinyl estradiol 35 µg over the last 10 days of CPA treatment versus spironolactone 200 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 79. Dexamethasone 0.37 mg/day versus dexamethasone 0.37 mg/day + spironolactone 100 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 80. Spironolactone 100 mg/day versus dexamethasone 0.37 mg/day + spironolactone 100 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 81. Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle + metformin 1000 mg b.i.d. versus metformin 1000 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 82. Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle + metformin 1000 mg b.i.d. versus clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 83. OCP (ethinyl estradiol 35 μg + norgestimate 0.25 mg) versus metformin 1000 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 84. OCP ethinyl estradiol 30 μg + desogestrel 0.15 mg) versus metformin 850 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 85. OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus metformin 850 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 86. OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) versus lifestyle modification

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 87. OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus sibutramine 10 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 88. OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus finasteride 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 89. OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) versus combined contraceptive vaginal ring (ethinyl estradiol 15 µg + etonogestrel 1.2 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 90. Finasteride 5 mg versus spironolactone 100 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 91. Flutamide 250 mg once to b.i.d. versus metformin 1275 mg to 1700 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change from baseline in Ferriman-Gallwey score	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Less than 12 month duration of study drug	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 12 month duration of study drug	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Changes in androgen levels			Other data	No numeric data

Comparison 92. Finasteride 5 mg once a day versus flutamide 250 mg once to b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of adverse events	3	115	Risk Ratio (M-H, Random, 95% CI)	3.87 [0.57, 26.24]
2 Mean change from baseline in Ferriman-Gallwey score	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Change in androgen levels			Other data	No numeric data

Comparison 93. Metformin 850 mg b.i.d. versus lifestyle modification

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 94. GnRH-A 3.75 mg im every 28 days versus OCP (ethinyl estradiol 35 μg + norethindrone 1 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 95. GnRH-A 3.75 mg im every 28 days versus OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 96. GnRH-A 3.75 mg im every 28 days versus OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 97. GnRH-A 3.75 mg im every 28 days versus finasteride 5 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 98. GnRH-A 3.6 mg im every 28 days versus metformin 850 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 99. Dexamethasone 0.37 mg per day compared to spironolactone 100 mg per day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 100. Spironolactone 25 mg b.i.d. versus metformin 500 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 101. Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle versus metformin 1000 mg b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in androgen levels			Other data	No numeric data

Comparison 102. Acarbose 150 mg to 300 mg per day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 103. Spearmint tea b.i.d. versus camomile tea b.i.d.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in androgen levels			Other data	No numeric data

Comparison 104. Low-frequency electro-acupuncture versus exercise 3 times a week for 30 minutes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Changes in androgen levels			Other data	No numeric data

Comparison 105. Low-frequency electro-acupuncture (14 treatments) versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in androgen levels			Other data	No numeric data

Comparison 106. Atorvastatin 20 mg once a day versus simvastatin 20 mg once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in androgen levels			Other data	No numeric data

Comparison 107. Atorvastatin 20 mg once a day versus placebo once a day

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in androgen levels			Other data	No numeric data

Comparison 108. Bromocriptine 2.5 mg three times a day versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in androgen levels			Other data	No numeric data

Analysis 1.1. Comparison 1 Exercise 3 times a week for 30 minutes versus no exercise, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in exercise group (standard deviation) N = 22 Jedel 2011; N = 45 Vigorito 2007	Mean change from baseline in control group (standard deviation) N = 13 Jedel 2011; N = 45 Vigorito 2007	Mean difference (95% CI; P value)
Jedel 2011	Testosterone (ng/ml)	-0.04 (0.14)	0.01 (0.09)	-0.05 (95% CI -0.13 to 0.03; P value = 0.20)
Jedel 2011	Free testosterone (pg/ml)	-1.24 (2.66)	0.03 (1.71)	-1.27 (95% CI -2.72 to 0.18; P value = 0.09)
Jedel 2011	Dihydrotestosterone (pg/ml)	-9.30 (34.2)	4.48 (31.9)	-13.78 (95% CI -36.25 to 8.69; P value = 0.23)
Jedel 2011	DHEAS (µg/ml)	-0.24 (0.55)	0.66 (3.40)	-0.90 (95% CI -2.96 to 0.34; P value = 0.34)

Changes in androgen levels (*Continued*)

Jedel 2011	SHBG (nmol/L)	7.30 (22.0)	3.33 (12.7)	3.97 (95% CI -7.53 to 15.47; P value = 0.50)
Vigorito 2007	Testosterone (nmol/L)	-0.20 (0.42)	-0.10 (0.30)	-0.10 (95% CI -0.25 to 0.05; P value = 0.19)
Vigorito 2007	DHEAS (µmol/L)	-152 (312.16)	-115 (267.94)	-37 (95% CI -157.20 to 83.20; P value = 0.55)
Vigorito 2007	Androstenedione (nmol/L)	-0.20 (0.48)	-0.20 (0.54)	0.00 (95% CI -0.21 to 0.21; P value = 1.00)
Vigorito 2007	SHBG (nmol/L)	2.00 (3.81)	-1.00 (4.25)	3.00 (95% CI 1.33 to 4.67; P value = 0.0004)
Vigorito 2007				

Analysis 2.1. Comparison 2 Lifestyle modification + placebo tablets versus placebo tablets, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in lifestyle modification group + placebo (standard deviation)** **N = 6** Hoeger 2004**;** **N = 8** Hoeger 2008	**Mean change from baseline in placebo group (standard deviation)** **N = 7** Hoeger 2004**;** **N = 10** Hoeger 2008	**Mean difference (95% CI; P value)**
Hoeger 2004	Testosterone (ng/dl)	1.7 (11.39)	4.8 (20.06)	-3.10 (95% CI -20.53 to 14.33; P value = 0.73)
Hoeger 2004	SHBG (nmol/L)	-4.74 (32.40)	-8.19 (7.22)	3.45 (95% CI -26.43 to 33.33; P value = 0.82)
Hoeger 2008	Testosterone (ng/dl)	0.60 (18.92)	10.40 (20.57)	-9.80 (95% CI -28.09 to 8.49; P value = 0.29)
Hoeger 2008	SHBG (nmol/L)	17.40 (13.86)	1.40 (5.64)	16.00 (95% CI 5.78 to 26.22; P value = 0.002)

Analysis 3.1. Comparison 3 Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + drospirenone 3 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + CPA group (standard deviation) N = 43** Batukan 2007**; N = 51** Bhattacharya 2012	**Mean change from baseline in EE + drospirenone group (standard deviation) N = 48** Batukan 2007**; N = 50** Bhattacharya 2012	**Mean Difference (95% CI; P value)**
Batukan 2007	Testosterone (ng/dl)	-20.30 (20.15)	-19.00 (18.73)	-1.30 (95% CI -9.32 to 6.72; P value = 0.75)
Batukan 2007	Free testosterone (pg/ml)	-0.40 (0.88)	-0.50 (0.93)	0.10 (95% CI -0.27 to 0.47; P value = 0.60)
Batukan 2007	DHEAS (μg/ml)	-0.20 (0.42)	-0.10 (0.88)	-0.10 (95% CI -0.38 to 0.18; P value = 0.48)
Batukan 2007	Androstenedione (ng/ml)	-0.50 (0.42)	-0.30 (0.44)	-0.20 (95% CI -0.38 to -0.02; P value = 0.03)
Batukan 2007	SHBG (nmol/L)	9 (8.71)	16.80 (20.15)	-7.80 (95% CI -14.07 to -1.53; P value = 0.01)
Bhattacharya 2012	Testosterone (ng/ml)	-0.03 (0.42)	-0.06 (0.32)	0.03 (95% CI -0.12 to 0.18; P value = 0.69)
Bhattacharya 2012	SHBG (nmol/L)	142.91 (60.71)	131.52 (72.89)	11.39 (95% CI -14.80 to 37.58; P value = 0.39)
Bhattacharya 2012	Free androgen index	-10.57 (7.93)	-7.89 (9.13)	-2.68 (95% CI -6.02 to 0.66; P value = 0.12)
Bhattacharya 2012				
Bhattacharya 2012				

Analysis 4.1. Comparison 4 Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg, Outcome 1 Mean change from baseline in Ferriman-Gallwey score.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 4 Ethinyl estradiol 35 μ g + cyproterone acetate 2 mg versus ethinyl estradiol 30 μ g + desogestrel 0.15 mg

Outcome: 1 Mean change from baseline in Ferriman-Gallwey score

Study or subgroup	EE + CPA N	Mean(SD)	EE + desogestrel N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bhattacharya 2012	51	-5.29 (5.88)	49	-1.69 (5.69)		38.2 %	-3.60 [-5.87, -1.33]
Mastorakos 2002	14	-9.78 (4.3)	14	-8.71 (3.86)		27.8 %	-1.07 [-4.10, 1.96]
Mastorakos 2006	18	-9.99 (3.24)	18	-9.51 (4.45)		34.0 %	-0.48 [-3.02, 2.06]
Total (95% CI)	**83**		**81**			**100.0 %**	**-1.84 [-3.86, 0.18]**

Heterogeneity: Tau² = 1.44; Chi² = 3.64, df = 2 (P = 0.16); I² =45%

Test for overall effect: Z = 1.78 (P = 0.075)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg, Outcome 2 Mean change from baseline in Lorenzo score.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 4 Ethinyl estradiol 35 μ g + cyproterone acetate 2 mg versus ethinyl estradiol 30 μ g + desogestrel 0.15 mg

Outcome: 2 Mean change from baseline in Lorenzo score

Study or subgroup	EE + CPA N	Mean(SD)	EE + desogestrel N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Porcile 1991	9	-7 (9.79)	10	-7.2 (1.84)		0.20 [-6.30, 6.70]

Analysis 4.3. Comparison 4 Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg, Outcome 3 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + CPA group (standard deviation) N = 51** Bhattacharya 2012**; N = 14** Mastorakos 2002**; N = 18** Mastorakos 2006; **N = 9** Porcile 1991	**Mean change from baseline in EE + desogestrel group (standard deviation) N = 49** Bhattacharya 2012**; N = 14** Mastorakos 2002**; N = 18** Mastorakos 2006**; N = 10** Porcile 1991	**Mean difference (95% CI; P value)**
Bhattacharya 2012	Testosterone (ng/ml)	-0.03 (0.42)	-0.10 (0.39)	-0.07 (95% CI -0.09 to 0.23; P value = 0.39)
Bhattacharya 2012	SHBG (nmol/L)	142.91 (60.71)	99.53 (67.52)	43.38 (95% CI 18.18 to 68.58; P value = 0.007)
Bhattacharya 2012	Free Androgen Index	-10.57 (7.93)	-5.58 (9.15)	-4.99 (95% CI -8.35 to -1.63; P value = 0.004)
Bhattacharya 2012				
Bhattacharya 2012				
Mastorakos 2002	Testosterone (ng/ml)	-0.43 (0.23)	-0.35 (0.18)	-0.08 (95% CI -0.23 to 0.07; P value = 0.31)
Mastorakos 2002	SHBG (nmol/L)	274.26 (47.39)	264.56 (54.69)	9.70 (95% CI -28.21 to 47.61; P value = 0.62)
Mastorakos 2002	Free testosterone (pg/ml)	-1.46 (0.68)	-1.57 (0.54)	0.11 (95% CI -0.34 to 0.56; P value = 0.64)
Mastorakos 2002	Androstenedione (ng/ml)	-1.16 (0.64)	-1.53 (0.60)	0.41 (95% CI -0.04 to 0.86; P value = 0.08)
Mastorakos 2002	DHEAS (ng/ml)	-472.67 (572.34)	-292.05 (808.65)	-180.62 (95% CI -6.99.57 to 338.33; P value =0.50)
Mastorakos 2006	Testosterone (ng/ml)	-0.48 (0.27)	-0.51 (0.24)	0.03 (95% CI -25.24 to 25.30; P value = 1.00)
Mastorakos 2006	SHBG (nmol/L)	309.03 (80.46)	287.22 (80.86)	21.81 (95% CI -30.89 to 74.51; P value = 0.42)

Changes in androgen levels (*Continued*)

Mastorakos 2006	Free testosterone (pg/ml)	-1.55 (2.12)	-1.50 (6.57)	-0.05 (95% CI -3.24 to 3.14; P value = 0.98)
Mastorakos 2006	Androstenedione (ng/ml)	-1.32 (0.97)	-1.66 (0.96)	0.34 (95% CI -0.29 to 0.97; P value = 0.29)
Mastorakos 2006	DHEAS (ng/ml)	-578.28 (915.49)	-321.61 (887.67)	-256.67 (95% CI -845.76 to 332.42; P value = 0.39)
Porcile 1991	Testosterone (nmol/L)	-1.52 (0.93)	-1.52 (0.93)	0.00 (95% CI -0.84 to 0.84; P value = 1.00)
Porcile 1991				
Porcile 1991	Free testosterone (pmol / L)	-10.06 (3.06)	-10.06 (3.06)	0.00 (95% CI -2.76 to 2.76; P value = 1.00)
Porcile 1991				
Porcile 1991	DHEAS (µmol/L)	-1.5 (2.10)	-3 (1)	1.50 (95% CI -0.01 to 3.01; P value = 0.05)

Analysis 5.1. Comparison 5 Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + drospirenone group (standard deviation) N= 50** Bhattacharya 2012**; N = 29** Kriplani 2010	**Mean change from baseline in EE + desogestrel group (standard deviation) N= 50** Bhattacharya 2012**; N = 29** Kriplani 2010	**Mean difference (95% CI; P value)**
Bhattacharya 2012	Testosterone (ng/ml)	-0.06 (0.32)	-0.10 (0.39)	0.04 (95% CI -0.10 to 0.18; P value = 0.58)
Bhattacharya 2012	SHBG (nmol/L)	131.52 (72.89)	99.53 (67.52)	31.99 (95% CI 4.32 to 59.66; P value = 0.02)
Bhattacharya 2012	Free Androgen Index	-7.89 (9.13)	-5.58 (9.15)	-2.31 (95% CI -5.91 to 1.29; P value = 0.21)
Kriplani 2010	Testosterone (ng/ml)	-0.10 (0.18)	0.0 (0.13)	-0.10 (95% CI -0.18 to -0.02; P value = 0.02)
Kriplani 2010	SHBG (nmol/L)	42.30 (41.33)	37.50 (29.13)	4.80 (95% CI -13.60 to 23.20; P value = 0.61)

Changes in androgen levels (*Continued*)

Kriplani 2010				

Analysis 6.1. Comparison 6 Ethinyl estradiol 35 μg + cyproterone acetate 2 mg versus other OCP (unknown), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + CPA group (standard deviation) N = 30**	**Mean change from baseline in OCP group (standard deviation) N = 30**	**Mean difference (95% CI; P value)**
Taheripanah 2010	Free testosterone (ng/ml)	-0.36 (4.93)	-0.24 (5.48)	-0.12 (95% CI -2.76 to 2. 52; P value = 0.93)
Taheripanah 2010	DHEAS (µg/ml)	0.12 (4.62)	-0.31 (5.38)	0.43 (95% CI -2.11 to 2. 97; P value = 0.74)

Analysis 7.1. Comparison 7 Ethinyl estradiol 35 µg + cyproterone acetate 2 mg versus ethinyl estradiol 50 µg + desogestrel 0.15 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + CPA group (standard deviation) N = 9**	**Mean change from baseline in EE50 + desogestrel group (standard deviation) N = 5**	**Mean difference (95% CI; P value)**
Porcile 1991	Testosterone (nmol/L)	-1.52 (0.93)	-1.52 (0.93)	0.00 (95% CI -1.02 to 1. 02; P value = 1.00)
Porcile 1991	Free testosterone (pmol /L)	-10.06 (3.06)	-10.06 (3.06)	0.00 (95% CI -3.35 to 3. 35; P value = 1.00)
Porcile 1991	DHEAS (µmol/L)	-1.5 (2.10)	-3 (0.77)	1.50 (95% CI -0.03 to 3. 03; P value = 0.05)

Analysis 8.1. Comparison 8 Ethinyl estradiol 30 µg + desogestrel 0.15 mg versus ethinyl estradiol 50 µg + desogestrel 0.15 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in EE30 + desogestrel group (standard deviation) N = 5	Mean change from baseline in EE50 + desogestrel group (standard deviation) N = 10	Mean Difference (95% CI; P value)
Porcile 1991	Testosterone (nmol/L)	-1.52 (0.93)	-1.52 (0.93)	0 (95% CI -1.00 to 1.00; P value = 1.00)
Porcile 1991	Free testosterone (pmol /L)	-10.06 (3.06)	-10.06 (3.06)	0 (95% CI -3.28 to 3.28; P value = 1.00)
Porcile 1991	DHEAS (µmol/L)	-3 (1)	-3 (0.77)	0 (95% CI -0.92 to 0.92; P value = 1.00)

Analysis 9.1. Comparison 9 Ethinyl estradiol 30 µg + desogestrel 0.15 mg versus ethinyl estradiol 30 µg and levonorgestrel 0.15 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in EE + desogestrel group (standard deviation) N = 11	Mean change from baseline in EE + levonorgestrel group (standard deviation) N = 10	Mean difference (95% CI; P value)
Breitkopf 2003	Testosterone (ng/ml)	-22.27 (12.65)	-0.48 (19.32)	-21.79 (95% CI -35.91 to -7.67; P value = 0.002)
Breitkopf 2003	Free testosterone (pg/ml)	-1.58 (1.20)	0.25 (2.64)	-1.83 (95% CI -3.61 to -0.05; P value = 0.04)
Breitkopf 2003	DHEAS (ng/ml)	-434 (481.69)	155 (747.82)	-589.00 (95% CI -1132.93 to -45.07; P value = 0.03)
Breitkopf 2003	SHBG (nmol/L)	59.05 (38.44)	11.06 (15.35)	47.99 (95% CI 23.36 to 72.62; P value = 0.0001)
Breitkopf 2003	Androstenedione (ng/ml)	-0.67 (0.58)	-0.60 (0.69)	-0.07 (95% CI -0.62 to 0.48; P value = 0.80)

Analysis 10.1. Comparison 10 Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 30 μg + chlormadinone acetate 2 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + drospirenone group (standard deviation) N = 30**	**Mean change from baseline in EE + chlormadinone group (standard deviation) N = 25**	**Mean Difference (95% CI; P value)**
Lello 2008	Androstenedione (ng/ml)	-2.44 (0.34)	-1.63 (0.28)	-0.81 (95% CI -0.97 to -0.65; P value < 0.001)
Lello 2008	DHEAS (μg/ml)	-0.77 (0.52)	-0.75 (0.52)	-0.02 (95% CI -0.30 to 0.26; P value = 0.89)
Lello 2008	Testosterone (nmol/L)	-1.09 (0.17)	-0.85 (0.17)	-0.24 (95% CI -0.33 to -0.15; P value < 0.001)
Lello 2008	SHBG (nmol/L)	143.93 (12.56)	144.73 (8.81)	-0.80 (95% CI -6.47 to 6.87; P value = 0.78)

Analysis 11.1. Comparison 11 Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 μg + desogestrel 0.15 mg every other month, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + desogestrel each month group (standard deviation) N = 9**	**Mean change from baseline in EE + desogestrel every other month group (standard deviation) N = 6**	**Mean difference (95% CI; P value)**
Porcile 1991B	Testosterone (nmol/L)	-0.65 (1.08)	-0.20 (1.23)	-0.45 (95% CI -1.66 to 0.76; P value = 0.47)
Porcile 1991B	Free testosterone (pmol/L)	-0.65 (3.85)	-0.30 (0.36)	-0.35 (95% CI -2.88 to -2.18; P value =0.79)

Analysis 12.1. Comparison 12 Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + desogestrel each month group (standard deviation) N = 10** Hoeger 2008**; N = 9** Porcile 1991B	**Mean change from baseline in placebo group (standard deviation) N = 10** Hoeger 2008**; N = 5** Porcile 1991B	**Mean Difference (95% CI; P value)**
Hoeger 2008	Testosterone (ng/dl)	-28.50 (17.16)	10.40 (20.57)	-38.90 (95% CI -55.50 to -22.30; P value < 0.001)
Hoeger 2008	SHBG (nmol/L)	75.20 (57.57)	1.40 (5.64)	73.80 (95% CI 37.95 to 109.65; P value < 0.001)
Porcile 1991B	Testosterone (nmol/L)	-0.65 (1.08)	0.05 (0.59)	-0.70 (95% CI -1.57 to 0.17; P value = 0.12)
Porcile 1991B	Free testosterone (pmol/L)	-0.65 (3.85)	-0.15 (0.15)	-0.50 (95% CI -3.02 to 2.02; P value = 0.70)

Analysis 13.1. Comparison 13 Ethinyl estradiol 30 μg + desogestrel 0.15 mg every other month versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in EE + desogestrel every other month group (standard deviation) N = 6**	**Mean change from baseline in placebo group (standard deviation) N = 5**	**Mean difference (95% CI; P value)**
Porcile 1991B	Testosterone (nmol/L)	-0.20 (1.23)	0.05 (0.59)	-0.25 (95% CI -1.36 to 0.86; P value = 0.66)
Porcile 1991B	Free testosterone (pmol/L)	-0.30 (0.36)	-0.15 (0.15)	-0.15 (95% CI -0.47 to 0.17; P value = 0.35)

Analysis 14.1. Comparison 14 Ethinyl estradiol 30 μg + desogestrel 0.15 mg versus ethinyl estradiol 30 μg + gestodene 75 μg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in EE + desogestrel group (standard deviation) N = 17	Mean change from baseline in EE + gestodene group (standard deviation) N = 17	Mean differences (95% CI; P value)
Sobbrio 1990	Total testosterone (ng/ml)	-0.13 (0.19)	-0.18 (0.17)	0.05 (95% CI -0.07 to 0.17; P value = 0.42)
Sobbrio 1990	Free testosterone (pg/ml)	-2.23 (0.91)	-1.93 (0.72)	-0.30 (95% CI -0.85 to 0.25; P value = 0.29)
Sobbrio 1990	Androstenedione (ng/ml)	-1.37 (0.92)	-0.97 (0.99)	-0.40 (95% CI -1.04 to 0.24; P value = 0.22)
Sobbrio 1990	DHEAS (μg/dl)	-111 (109.55)	-112 (72.27)	1.00 (95% CI -61.39 to 63.39; P value = 0.97)
Sobbrio 1990	SHBG (nmol/L)	128 (73.11)	110 (60.83)	18 (95% CI -27.21 to 63.21; P value = 0.44)

Analysis 15.1. Comparison 15 Ethinyl estradiol 30 μg + drospirenone 3 mg versus ethinyl estradiol 20 μg + drospirenone 3 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in EE 30+ drospirenone group (standard deviation) N = 24	Mean change from baseline in EE 20 + drospirenone group (standard deviation) N = 23	Mean difference (95% CI; P value)
Oner 2011	Total testosterone (ng/dl)	-28.80 (28.90)	-19.50 (24.63)	-9.30 (95% CI -24.63 to 6.03; P value = 0.23)
Oner 2011	Free testosterone (pg/ml)	-0.80 (0.58)	-0.70 (0.48)	-0.10 (95% CI -0.40 to 0.20; P value = 0.52)
Oner 2011	Androstenedione (ng/ml)	-0.10 (0.18)	-0.10 (0.23)	0 (95% CI -0.12 to 0.12; P value = 1.00)
Oner 2011	DHEAS (μg/ml)	0.00 (1.24)	0.00 (0.86)	0 (95% CI -0.61 to 0.61; P value = 1.00)

Changes in androgen levels (*Continued*)

Oner 2011	SHBG (nmol/L)	17.50 (18.72)	22.00 (38.92)	-4.50 (95% CI -22.08 to 13.08; P value = 0.62)

Analysis 16.1. Comparison 16 Flutamide 250 mg b.i.d. versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide group (standard deviation) N = 17** Gambineri 2006**; N = 10** Moghetti 2000	**Mean change from baseline in placebo group (standard deviation) N = 19** Gambineri 2006**; N = 10** Moghetti 2000	**Mean difference (95% CI; P value)**
Gambineri 2006	Total testosterone (nmol/L)	-0.22 (0.14)	-0.15 (0.18)	-0.07 (95% CI -0.17 to 0.03; P value = 0.19)
Gambineri 2006	Androstenedione (nmol/L)	-161 (100.24)	-62.00 (73.29)	-99.00 (95% CI -156.94 to -41.06; P value = 0.0008)
Gambineri 2006	DHEAS (μmol/ml)	-1.40 (0.94)	0.40 (0.72)	-1.80 (95% CI -2.35 to -1.25; P value < 0.001)
Gambineri 2006	SHBG (nmol/L)	3.00 (6.79)	1.50 (11.02)	1.50 (95% CI -4.41 to 7.41; P value = 0.62)
Moghetti 2000	Free testosterone (pg/ml)	-0.58 (0.90)	0.04 (0.62)	-0.62 (95% CI -1.30 to 0.06; P value = 0.07)
Moghetti 2000	DHEAS (µgram/L)	-613 (438.41)	-451 (451.51)	-162.00 (95% CI -552.06 to 228.06; P value = 0.42)
Moghetti 2000	Testosterone (nmol/L)	-0.05 (0.44)	0.10 (0.31)	-0.05 (95% CI -0.38 to 0.28; P value = 0.77)
Moghetti 2000	Androstenedione (nmol/L)	-2.7 (3.36)	1.40 (3.42)	-4.10 (95% CI -7.07 to -1.13; P value = 0.007)

Analysis 17.1. Comparison 17 Flutamide 250 mg b.i.d. versus spironolactone 100 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide group (standard deviation) N = 10** Erenus 1994**; N = 10** Moghetti 2000	**Mean change from baseline in spironolactone group (standard deviation) N = 10** Erenus 1994**; N = 10** Moghetti 2000	**Mean difference (95% CI; P value)**
Erenus 1994	Testosterone (ng/dl)	-10.49 (10.99)	-6.70 (6.81)	-3.97 (95% CI -11.80 to 4.22; P value = 0.35)
Erenus 1994	DHEAS (mg/dl)	-38.00 (50.81)	-117.5 (86.56)	79.50 (95% CI 17.29 to 191.71; P value = 0.01)
Erenus 1994				
Erenus 1994				
Moghetti 2000	Free testosterone (pg/ml)	-0.58 (0.90)	-0.04 (0.59)	-0.54 (95% CI -1.21 to 0.13; P value = 0.11)
Moghetti 2000	DHEAS (µgram/L)	-613 (438.41)	159 (607.07)	-772.00 (95% CI -1236.12 to -307.88; P value = 0.001)
Moghetti 2000	Testosterone (nmol/L)	-0.05 (0.44)	-0.02 (0.42)	-0.03 (95% CI -0.41 to 0.35; P value = 0.88)
Moghetti 2000	Androstenedione (nmol/L)	-2.7 (3.36)	1.20 (4.56)	-3.90 (95% CI -7.41 to -0.39; P value = 0.03)

Analysis 18.1. Comparison 18 Spironolactone 100 mg per day versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in spironolactone group (standard deviation) N = 10**	**Mean change from baseline in placebo group (standard deviation) N = 10**	**Mean difference (95% CI; P value)**
Moghetti 2000	Free testosterone (pg/ml)	-0.04 (0.59)	0.04 (0.62)	0.00 (95% CI -0.53 to 0.53; P value = 1.00)

Changes in androgen levels (*Continued*)

Moghetti 2000	DHEAS (µgram/L)	159 (607.07)	-451 (451.51)	610.00 (95% CI 141.08 to 1078.92; P value = 0.01)
Moghetti 2000	Testosterone (nmol/L)	-0.02 (0.42)	0.10 (0.31)	-0.12 (95% CI -0.44 to 0. 20; P value = 0.47)
Moghetti 2000	Androstenedione (nmol/ L)	1.20 (4.56)	1.40 (3.42)	-0.20 (95% CI -3.73 to 3. 33; P value = 0.91)

Analysis 19.1. Comparison 19 Ketoconazole 400 mg per day versus ketoconazole 800 mg per day for 10 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in ketoconazole 400 mg group (standard deviation)**	**Mean change from baseline in ketoconazole 800 mg group (standard deviation)**	**Mean difference (95% CI; P value)**
Cedeno 1990	Free testosterone (pg/ml)	-5.77 (12.13)	-10.58 (12.52)	4.81 (95% CI -6.58 to 16. 20; P value = 0.41)
Cedeno 1990	DHEAS (µg/ml)	-79.77 (147.97)	-162.18 (174.22)	82.41 (95% CI -31.69 to 196.51; P value = 0.16)
Cedeno 1990	Androstenedione (ng/ml)	-0.11 (0.84)	-1.04 (1.27)	0.93 (95% CI -0.06 to 1. 92; P value = 0.07)

Analysis 20.1. Comparison 20 Finasteride 5 mg to 7.5 mg/day versus placebo, Outcome 1 Adverse events.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 20 Finasteride 5 mg to 7.5 mg/day versus placebo

Outcome: 1 Adverse events

Study or subgroup	Finasteride n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ciotta 1995	6/9	7/9		75.9 %	0.86 [0.48, 1.53]
Lakryc 2003	3/16	1/18		13.9 %	3.38 [0.39, 29.28]
Moghetti 2000	1/5	1/10		10.3 %	2.00 [0.16, 25.75]
Total (95% CI)	**30**	**37**		**100.0 %**	**1.13 [0.48, 2.67]**

Total events: 10 (Finasteride), 9 (Placebo)

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 2.43$, df = 2 (P = 0.30); $I^2 = 18\%$

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable

Analysis 20.2. Comparison 20 Finasteride 5 mg to 7.5 mg/day versus placebo, Outcome 2 Mean change from baseline in Ferriman-Gallwey score.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 20 Finasteride 5 mg to 7.5 mg/day versus placebo

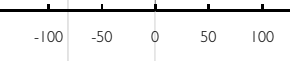
Outcome: 2 Mean change from baseline in Ferriman-Gallwey score

Study or subgroup	Finasteride N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ciotta 1995	9	-8 (2.93)	9	-1.8 (1.51)		28.2 %	-6.20 [-8.35, -4.05]
Lakryc 2003	12	-6.1 (2.02)	12	-0.8 (1.92)		52.6 %	-5.30 [-6.88, -3.72]
Moghetti 2000	10	-5.4 (2.6)	10	0.8 (3.32)		19.2 %	-6.20 [-8.81, -3.59]
Total (95% CI)	**31**		**31**			**100.0 %**	**-5.73 [-6.87, -4.58]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.59$, df = 2 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 9.81 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 20.3. Comparison 20 Finasteride 5 mg to 7.5 mg/day versus placebo, Outcome 3 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride group (standard deviation)** **N = 9** Ciotta 1995**;** **N =12** Lakryc 2003**;** **N = 10** Moghetti 2000	**Mean change from baseline in placebo group (standard deviation)** **N = 9** Ciotta 1995**;** **N =12** Lakryc 2003**;** **N = 10** Moghetti 2000	**Mean difference (95% CI; P value)**
Ciotta 1995	Total testosterone (ng/ml)	0.23 (0.09)	0.13 (0.13)	0.10 (95% CI 0.00 to 0.20; P value = 0.06)
Ciotta 1995	Free testosterone (pg/ml)	0.18 (0.20)	0.22 (0.16)	-0.04 (95% CI -0.21 to 0.13; P value = 0.64)
Ciotta 1995	Androstenedione (ng/ml)	-0.01 (0.22)	0.11 (0.29)	-0.12 (95% CI -0.36 to 0.12; P value = 0.32)
Ciotta 1995	Dihydrotestosterone (pg/ml)	-210 (53.96)	-54.40 (90.39)	-155.60 (95% CI -224.38 to -86.82; P < 0.001)
Ciotta 1995	DHEAS (μg/ml)	-0.17 (0.19)	0.17 (0.36)	-0.34 (95% CI -0.61 to -0.07; P value = 0.01)
Ciotta 1995	SHBG (μg/ml)	-0.30 (0.24)	-0.26 (0.30)	-0.04 (95% CI -0.29 to 0.21; P value = 0.75)
Lakryc 2003	Total testosterone (ng/ml)	-3.10 (19.21)	10.10 (28.80)	-13.20 (95% CI -32.79 to 6.39; P value = 0.19)
Lakryc 2003	Free testosterone (nmol/L)	-1.20 (2.96)	-0.10 (2.91)	-1.10 (95% CI -3.45 to 1.25; P value = 0.36)
Lakryc 2003	Androstenedione (ng/ml)	0.10 (0.44)	-0.10 (0.66)	0.20 (95% CI -0.25 to 0.65; P value = 0.38)
Lakryc 2003	Dihydrotestosterone (ng/ml)	-0.41 (0.11)	0 (0.06)	-0.41 (95% CI -0.48 to -0.34; P < 0.001)
Lakryc 2003	DHEAS (μg/ml)	-0.50 (0.64)	-0.20 (0.64)	-0.30 (95% CI -0.81 to 0.21; P value = 0.25)
Lakryc 2003				

Changes in androgen levels (*Continued*)

Moghetti 2000	Free testosterone (pg/ml)	0.74 (0.83)	0.04 (0.62)	0.70 (95% CI 0.06 to 1.34; P value = 0.03)
Moghetti 2000	DHEAS (µgram/L)	-301 (358.81)	-451 (451.51)	150.00 (95% CI -207.45 to 507.45; P value = 0.41)
Moghetti 2000	Testosterone (nmol/L)	0.56 (0.34)	0.10 (0.31)	0.46 (95% CI 0.17 to 0.75; P value = 0.002)
Moghetti 2000	Androstenedione (nmol/L)	1.70 (2.58)	1.40 (3.42)	0.30 (95% CI -2.36 to 2.96; P value = 0.82)
Moghetti 2000				
Moghetti 2000				

Analysis 21.1. Comparison 21 Finasteride 2.5 mg once a day versus finasteride 5 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride 2.5 mg group (standard deviation)** **N = 15** Al-Khawajah 1998**;** **N = 29** Bayram 2002	**Mean change from baseline in finasteride 5 mg group (standard deviation)** **N = 15** Al-Khawajah 1998**;** **N = 27** Bayram 2002	**Mean difference (95% CI; P value)**
Al-Khawajah 1998	Testosterone (nmol/l)	0.22 (0.36)	0.25 (0.38)	-0.03 (-0.29 to 0.23; P value = 0.82)
Al-Khawajah 1998	DHT (ng/ml)	-2.08 (3.88)	-2.24 (3.48)	0.16 (95% CI -2.48 to 2.80; P value = 0.91)
Al-Khawajah 1998	Free testosterone	Authors stated no statistically significant changes compared to baseline	Authors stated no statistically significant changes compared to baseline	Cannot be calculated
Al-Khawajah 1998	DHEAS	Authors stated no statistically significant changes compared to baseline	Authors stated no statistically significant changes compared to baseline	Cannot be calculated
Al-Khawajah 1998				
Bayram 2002	Testosterone (ng/dl)	0.70 (30.07)	2.90 (30.99)	-2.20 (95% CI -18.21 to 13.81; P value = 0.79)

Changes in androgen levels (*Continued*)

Bayram 2002	Free testosterone (pg/ml)	0 (0.91)	-0.20 (1.26)	0.20 (95% CI -0.38 to 0.78; P value = 0.50)
Bayram 2002	Androstenedione (ng/ml)	0.10 (1.05)	-0.40 (0.84)	0.50 (95% CI 0 to 1.00; P value = 0.05)
Bayram 2002	SHBG (nmol/L)	1.30 (18.95)	3.80 (10.97)	-2.50 (95% CI -10.54 to 5.54; P value = 0.54)
Bayram 2002	DHEAS (mg/dl)	28.90 (95.35)	-13.80 (89.55)	42.70 (95% CI -5.73 to 91.13; P value = 0.08)

Analysis 22.1. Comparison 22 Finasteride 2.5 mg once a day versus finasteride 7.5 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride 2.5 mg group (standard deviation) N = 15**	**Mean change from baseline in finasteride 7.5 mg group (standard deviation) N = 15**	**Mean difference (95% CI; P value)**
Al-Khawajah 1998	Testosterone (nmol/l)	0.22 (0.36)	0.15 (0.46)	0.07 (95% CI -0.23 to 0.37; P value = 0.64)
Al-Khawajah 1998	Dihydrotestosterone (ng/ml)	-2.08 (3.88)	-1.29 (3.54)	-0.79 (95% CI -3.45 to 1.87; P value = 0.56)
Al-Khawajah 1998	Free testosterone	Authors stated no statistically significant changes compared to baseline	Authors stated no statistically significant changes compared to baseline	Cannot be calculated
Al-Khawajah 1998	DHEAS	Authors stated no statistically significant changes compared to baseline	Authors stated no statistically significant changes compared to baseline	Cannot be calculated

Analysis 23.1. Comparison 23 Finasteride 5 mg once a day versus finasteride 7.5 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride 5 mg group (standard deviation) N = 15**	**Mean change from baseline in finasteride 7.5 mg group (standard deviation) N = 15**	**Mean difference (95% CI; P value)**
Al-Khawajah 1998	Testosterone (nmol/l)	0.25 (0.38)	0.15 (0.46)	0.10 (95% CI -0.12 to 0. 32; P value = 0.37)
Al-Khawajah 1998	Dihydrotestosterone (ng/ ml)	-2.24 (3.48)	-1.29 (3.54)	-0.95 (95% CI -3.46 to 1. 56; P value =0.46)
Al-Khawajah 1998	Free testosterone	Authors stated no statistically significant changes compared to baseline	Authors stated no statistically significant changes compared to baseline	Cannot be calculated
Al-Khawajah 1998	DHEAS	Authors stated no statistically significant changes compared to baseline	Authors stated no statistically significant changes compared to baseline	Cannot be calculated

Analysis 24.1. Comparison 24 Finasteride 2.5 mg once a day versus finasteride 2.5 mg every 3 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride 2.5 mg group (standard deviation) N = 19**	**Mean change from baseline in finasteride 2.5 mg every 3 days group (standard deviation) N = 19**	**Mean difference (95% CI; P value)**
Tartagni 2004	Total testosterone (ng/dl)	-0.19 (1.38)	-0.14 (2.24)	-0.05 (95% CI -1.23 to 1. 13; P value = 0.93)
Tartagni 2004	Dihydrotestosterone ng/ dl)	-21.47 (0.53)	-20.98 (0.54)	-0.49 (95% CI -0.83 to -0. 15; P value = 0.005)
Tartagni 2004	DHEAS (µg/ml)	0.35 (0.78)	0.54 (0.8)	-0.19 (95% CI -0.69 to 0. 31; P value = 0.46)
Tartagni 2004	SHBG (µg/ml)	-0.02 (0.99)	-0.14 (1.11)	0.12 (95% CI -0.55 to 0. 79; P value = 0.73)
Tartagni 2004	Androstenedione (ng/ml)	-0.02 (0.83)	-0.03 (0.55)	-0.01 (95% CI -0.44 to 0. 46; P value = 0.97)

Analysis 25.1. Comparison 25 Metformin 850 mg b.i.d. versus rosiglitazone 2 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin group (standard deviation) N = 31**	**Mean change from baseline in rosiglitazone group (standard deviation) N = 30**	**Mean difference (95% CI; P value)**
Ahmad 2008	Testosterone (pg/ml)	-0.66 (0.44)	-0.67 (0.39)	0.01 (95% CI -0.20 to 0.22; P value = 0.93)
Ahmad 2008	DHEAS (µg/ml)	-56.30 (19.56)	-57.69 (17.20)	1.39 (95% CI -7.85 to 10. 63; P value =0.77)
Ahmad 2008	Androstenedione (ng/ml)	-1.44 (0.53)	-0.39 (0.30)	-1.05 (95% -1.27 to -0.83; P value < 0.001)

Analysis 26.1. Comparison 26 Troglitazone 150 mg versus troglitazone 300 mg versus troglitazone 600 mg versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in troglitazone 150 mg group (standard deviation) N = 78**	**Mean change from baseline in troglitazone 300 mg group (standard deviation) N = 77**	**Mean change from baseline in troglitazone 600 mg group (standard deviation) N = 78**	**Mean change from baseline in placebo group (standard deviation) N = 73**
Azziz 2001	Total testosterone (ng/mL)	-0.06 (0.26)	-0.01 (0.26)	-0.01 (0.26)	-0.04 (0.26)
Azziz 2001	Free testosterone (pg/mL)	-2.72 (4.86)	-3.07 (4.83)	-4.13 (4.86)	-1.11 (4.87)
Azziz 2001	Androstenedione (ng/mL)	-0.16 (0.53)	-0.11 (0.53)	-0.14 (0.53)	-0.01 (0.51)
Azziz 2001	SHBG (nmol/L)	-8.05 (21.90)	-18.69 (21.85)	-29.12 (21.99)	-2.22 (21.96)

Analysis 27.1. Comparison 27 Metformin 500 mg to 1500 mg per day versus placebo for 12 to 48 weeks, Outcome 1 Mean change from baseline in Ferriman-Gallwey score.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 27 Metformin 500 mg to 1500 mg per day versus placebo for 12 to 48 weeks

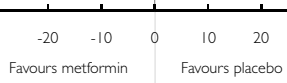
Outcome: 1 Mean change from baseline in Ferriman-Gallwey score

Study or subgroup	Metformin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Gambineri 2006	20	-2.6 (5.37)	19	-1.3 (2.89)		19.4 %	-1.30 [-3.99, 1.39]
Hoeger 2004	5	-1.9 (9.49)	7	0.6 (2.58)		1.9 %	-2.50 [-11.03, 6.03]
Hoeger 2008	6	0.4 (2.04)	10	-0.9 (3.25)		20.9 %	1.30 [-1.29, 3.89]
Maciel 2004	15	-0.1 (3.6)	14	0.5 (3.6)		20.4 %	-0.60 [-3.22, 2.02]
Moghetti 2000B	12	0.7 (3.37)	11	1.8 (3.9)		15.7 %	-1.10 [-4.09, 1.89]
Onalan 2005	55	6.2 (50.06)	61	9.6 (20.2)		0.7 %	-3.40 [-17.57, 10.77]
Otta 2010	14	-0.13 (3.35)	15	-0.5 (3.77)		20.9 %	0.37 [-2.22, 2.96]
Total (95% CI)	**127**		**137**			**100.0 %**	**-0.27 [-1.46, 0.91]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.01$, df = 6 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.45 (P = 0.65)

Test for subgroup differences: Not applicable



Analysis 27.2. Comparison 27 Metformin 500 mg to 1500 mg per day versus placebo for 12 to 48 weeks, Outcome 2 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in metformin group (standard deviation) N = 19 Eisenhardt 2006; N = 20 Gambineri 2006; N = 5 Hoeger 2004; N = 6 Hoeger 2008; N = 15 Maciel 2004; N =12 Moghetti 2000B; N = 55 Onalan 2005; N = 14 Otta 2010	Mean change from baseline in placebo group (standard deviation) N = 19 Eisenhardt 2006; N = 19 Gambineri 2006; N = 7 Hoeger 2004; N = 10 Hoeger 2008; N = 14 Maciel 2004; N =11 Moghetti 2000B; N = 61 Onalan 2005; N = 15 Otta 2010	Mean difference (95% CI; P value)
Eisenhardt 2006	DHEAS (µmol/L)	Median change from baseline 0.19 (SD cannot be calculated)	Median change from baseline 0.78 (SD cannot be calculated)	Cannot be calculated

Changes in androgen levels (*Continued*)

Eisenhardt 2006	Testosterone (nmol/L)	Median change from baseline 0 (SD cannot be calculated)	Median change from baseline -0.13 (SD cannot be calculated)	Cannot be calculated
Eisenhardt 2006	Androstenedione (nmol/L)		Median change from baseline 3.37 (SD cannot be calculated)	Cannot be calculated
Eisenhardt 2006	SHBG (nmol/L)	Median change from baseline 1.4 (SD cannot be calculated)	Median change from baseline 1.4 (SD cannot be calculated)	Cannot be calculated
Gambineri 2006	Total testosterone (nmol/L)	-0.15 (0.22)	-0.15 (0.18)	0.0 (95% CI -0.13 to 0.13; P value = 1.00)
Gambineri 2006	Androstenedione (nmol/L)	-51 (103.72)	-62.00 (73.29)	11 (95% CI -45.15 to 67.15; P value = 0.70)
Gambineri 2006	DHEAS (μmol/ml)	0.10 (0.36)	0.40 (0.72)	-0.30 (95% CI -0.66 to 0.06; P value = 0.10)
Gambineri 2006	SHBG (nmol/L)	2.20 (7.69)	1.50 (11.02)	0.70 (95% CI -5.29 to 6.69; P value = 0.82)
Hoeger 2004	Testosterone (ng/dl)	4.0 (16.75)	4.8 (20.06)	-0.80 (95% CI -21.92 to 20.09; P value = 0.94)
Hoeger 2004	SHBG (nmol/L)	0.48 (34.05)	-8.19 (7.22)	8.67 (95% CI -21.65 to 38.99; P value = 0.58)
Hoeger 2004				
Hoeger 2004				
Hoeger 2008	Testosterone (ng/dl)	-1.60 (22.12)	10.40 (20.57)	-12.00 (95% CI -33.81 to 9.81; P value = 0.28)
Hoeger 2008	SHBG (nmol/L)	-2.40 (13.37)	1.40 (5.64)	-3.80 (95% CI -15.05 to 7.45; P value = 0.51)
Hoeger 2008				
Hoeger 2008				
Maciel 2004	Testosterone (ng/dL)	-23.9 (17.3)	3.1 (30)	-27.00 (95% CI -44.99 to -9.01; P value = 0.003)

Changes in androgen levels (*Continued*)

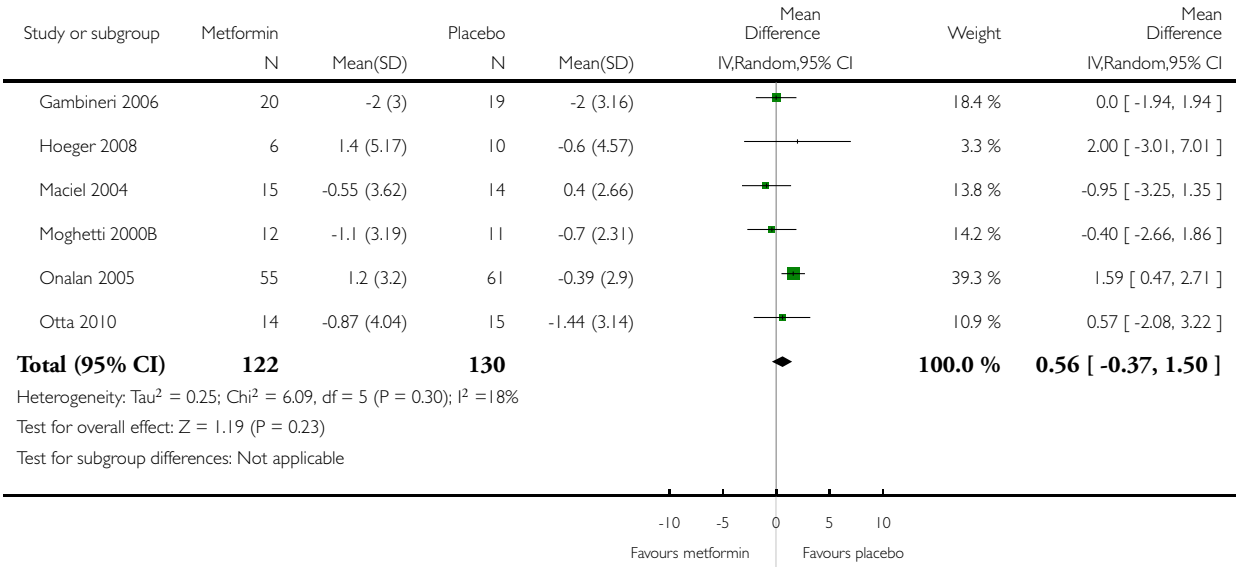
Maciel 2004	Free testosterone (pg/dL)	-1.7 (1.4)	0.1 (0.8)	-1.8 (95% CI -2.62 to -0.98; P value < 0.001)
Maciel 2004	Androstenedione (ng/dL)	-0.55 (0.49)	0.1 (0.7)	-0.65 (95% CI -1.09 to -0.21; P value = 0.004)
Maciel 2004	SHBG (nmol/L)	13.3 (54.5)	46.1 (63.3)	-32.80 (95% CI -75.93 to 10.33; P value = 0.14)
Moghetti 2000B	Free testosterone (pmol/L)	-2.90 (3.75)	-0.30 (3.39)	-2.60 (95% CI -5.52 to 0.32: P value = 0.08)
Moghetti 2000B	Androstenedione (nmol/L)	1.10 (4.41)	0.40 (2.02)	0.70 (95% CI -2.07 to 3.47; P value = 0.62)
Moghetti 2000B	DHEAS (µmol/L)	0.60 (1.46)	-0.30 (0.99)	0.90 (95% CI -0.11 to 1.91; P value = 0.08)
Moghetti 2000B	SHBG (nmol/L)	9 (22.05)	0.90 (11.96)	8.10 (95% -6.24 to 22.44; P value = 0.27)
Onalan 2005	Free testosterone (pg/ml)	20.6 (12.6)	9.0 (15.2)	-11.60 (95% CI 6.54 to 16.66; P < 0.001)
Onalan 2005	SHBG (nmol/ml)	23.3 (60.7)	-24. 4 (96.4)	47.70 (95% CI 18.67 to 76.32; P value = 0.001)
Onalan 2005	Androstenedione (ng/dl)	21.5 (15.8)	7.3 (11.6)	14.20 (95% CI 9.11 to 19.29; P value < 0.001)
Onalan 2005	DHEAS (µg/dl)	6.32 (21.55)	-4.78 (28.54)	11.10 (95% CI 1.95 to 20.25; P value = 0.02)
Otta 2010	Testosterone (ng/dl)	-16.84 (13.80)	-6.27 (14.99)	-10.57 (95% CI -21.05 to -0.09; P value = 0.05)
Otta 2010	DHEAS (µgram/dl)	2 (39.4)	-26 (79.14)	28 (95% -17.05 to 73.05; P value = 0.22)
Otta 2010	Androstenedione (ng/ml)	-0.29 (0.73)	-0.02 (0.87)	-0.27 (95% CI -0.85 to 0.31; P value = 0.36)
Otta 2010				

Analysis 27.3. Comparison 27 Metformin 500 mg to 1500 mg per day versus placebo for 12 to 48 weeks, Outcome 3 Mean change from baseline in BMI.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 27 Metformin 500 mg to 1500 mg per day versus placebo for 12 to 48 weeks

Outcome: 3 Mean change from baseline in BMI



Analysis 28.1. Comparison 28 Rosiglitazone 4 mg b.i.d. versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in rosiglitazone group (standard deviation) N = 24 Lam 2011; N = 12 Rautio 2005**	**Mean change from baseline in placebo group (standard deviation) N = 30 Lam 2011; N = 14 Rautio 2005**	**Mean difference (95% CI; P value)**
Lam 2011	Total testosterone (nmol/L)	-0.39 (0.82)	-0.42 (0.69)	0.03 (95% CI -0.38 to 0.43; P value = 0.89)
Lam 2011	SHBG (nmol/L)	2.5 (18.07)	4.3 (19.22)	-1.80 (95% CI -11.78 to 8.18; P value = 0.72)
Lam 2011	Free testosterone (nmol/L)	-0.007 (0.02)	-0.009 (0.02)	0.0 (95% CI -0.01 to 0.01; P value = 0.72)
Lam 2011				

Changes in androgen levels (*Continued*)

Rautio 2005	Testosterone (nmol/L)	0 (0.46)	-0.30 (0.71)	0.30 (95% CI -0.15 to 0. 75; P value = 0.20)
Rautio 2005	SHBG (nmol/L)	6.60 (11.12)	-2.40 (12.02)	9.00 (95% CI 0.10 to 17. 90; P value = 0.05)
Rautio 2005	Androstenedione (nmol/L)	-2.70 (3.95)	0.50 (3.85)	-3.20 (95% CI -6.21 to 0. 19; P value = 0.04)
Rautio 2005	DHEAS (µmol/L)	-0.78 (2.74)	0.20 (1.81)	-0.98 (95% CI -2.80 to 0. 84; P value = 0.29)

Analysis 29.1. Comparison 29 Metformin 850 mg b.i.d. versus simvastatin 20 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin group (standard deviation) N = 33**	**Mean change from baseline in simvastatin group (standard deviation) N = 28**	**Mean difference (95% CI; P value)**
Banaszewska 2011	Total testosterone (ng/ml)	-0.15 (0.23)	-0.22 (0.16)	0.07 (95% CI -0.03 to 0. 17; P value = 0.16)
Banaszewska 2011	Free testosterone (ng/dl)	-0.30 (0.46)	-0.28 (0.32)	-0.02 (95% CI -0.22 to 0. 18; P value = 0.84)
Banaszewska 2011	DHEAS (µmol/ml)	0.54 (2.13)	-1.64 (2.28)	2.18 (95% CI 1.07 to 3. 29; P value = 0.001)
Banaszewska 2011	SHBG (nmol/L)	2.27 (13.04)	-5.19 (11.64)	7.46 (95% CI 1.26 to 13. 66; P value = 0.02)

Analysis 30.1. Comparison 30 Pioglitazone 30 mg once a day versus placebo once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in pioglitazone group (standard deviation) N = 17**	**Mean change from baseline in placebo group (standard deviation) N = 18**	**Mean difference (95% CI; P value)**
Aigner 2009	DHEAS (μmol/L)	0.40 (1.74)	0.50 (1.53)	-0.10 (95% CI -1.19 to 0. 99; P value = 0.86)

Changes in androgen levels (*Continued*)

Aigner 2009	Testosterone (nmol/L)	-0.30 (0.76)	-0.30 (0.54)	0.0 (95% CI -0.44 to 0.44; P value = 1.00)
Aigner 2009	Free androgen index (U)	-2.9 (5.91)	1.3 (5.09)	-4.20 (95% CI -7.86 to -0.54; P value = 0.02)
Aigner 2009	SHBG (nmol/L)	4.0 (10.65)	-5.1 (22.55)	9.10 (95% CI -2.48 to 20.68; P value = 0.12)

Analysis 31.1. Comparison 31 Lifestyle modification + metformin 850 mg b.i.d. versus metformin 850 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in lifestyle modification + metformin group (standard deviation) N = 5**	**Mean change from baseline in metformin group (standard deviation) N = 5**	**Mean difference (95% CI; P value)**
Hoeger 2004	Testosterone (ng/dl)	-18.5 (10.26)	4.0 (16.75)	-22.50 (95% CI -39.72 to -5.28; P value = 0.01)
Hoeger 2004	SHBG (nmol/L)	-1.01 (31.12)	0.48 (34.05)	-1.49 (95% CI -41.92 to 38.94; P value = 0.94)

Analysis 32.1. Comparison 32 Lifestyle modification + placebo versus metformin 850 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in lifestyle modification + placebo group (standard deviation) N = 6**	**Mean change from baseline in metformin group (standard deviation) N = 5**	**Mean difference (95% CI; P value)**
Hoeger 2004	Testosterone (ng/dl)	1.7 (11.39)	4.0 (16.75)	-2.30 (95% CI -19.58 to 14.98; P value = 0.79)
Hoeger 2004	SHBG (nmol/L)	-4.74 (32.40)	0.48 (34.05)	-5.22 (95% CI -44.75 to 34.31; P value = 0.80)

Analysis 33.1. Comparison 33 Lifestyle modification + metformin 850 mg b.i.d. versus lifestyle modification + placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in lifestyle modification + metformin group (standard deviation) N = 5**	**Mean change from baseline in lifestyle + placebo group (standard deviation) N = 6**	**Mean difference (95% CI; P value)**
Hoeger 2004	Testosterone (ng/dl)	-18.5 (10.26)	1.7 (11.39)	-20.20 (95% CI -33.00 to -7.40; P value = 0.002)
Hoeger 2004	SHBG (nmol/L)	-1.01 (31.12)	-4.74 (32.40)	3.73 (95% CI -33.90 to 41.36; P value = 0.85)

Analysis 34.1. Comparison 34 Lifestyle modification + metformin 850 mg b.i.d. versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in lifestyle modification + metformin group (standard deviation) N = 5**	**Mean change from baseline in placebo group (standard deviation) N = 7**	**Mean difference (95% CI; P value)**
Hoeger 2004	Testosterone (ng/dl)	-18.5 (10.26)	4.8 (20.06)	-23.30 (95% CI -40.67 to -5.93; P value = 0.009)
Hoeger 2004	SHBG (nmol/L)	-1.01 (31.12)	-8.19 (7.22)	7.18 (95% CI -20.62 to 34.98; P value = 0.61)

Analysis 35.1. Comparison 35 Metformin 2000 mg per day + lifestyle modification + OCP versus placebo + lifestyle modification + OCP, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin group (standard deviation) N = 16**	**Mean changes from baseline in placebo group (standard deviation) N = 16**	**Mean difference (95% CI; P value)**
Hoeger 2008	Testosterone (ng/dl)	-27.50 (19.58)	-57.70 (13.77)	30.20 (95% CI 18.47 to 41.93; P value < 0.001)
Hoeger 2008	SHBG (nmol/L)	58.50 (46.83)	72.80 (44.17)	-14.30 (95% CI -45.84 to 17.24; P value = 0.37)

Analysis 36.1. Comparison 36 OCP (ethinyl estradiol 20 µg + desogestrel 0.15 mg) + simvastatin 20 mg versus OCP (ethinyl estradiol 20 µg + desogestrel 0.15 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + simvastatin group (standard deviation) N = 24**	**Mean change from baseline in OCP group (standard deviation) N = 24**	**Mean difference (95% CI; P value)**
Banaszewska 2007	Total testosterone (ng/ml)	-0.34 (0.14)	-0.11 (0.21)	-0.23 (95% CI -0.33 to -0.13; P value < 0.001)
Banaszewska 2007	Free testosterone (pg/ml)	-0.54 (0.47)	-0.36 (0.62)	-0.18 (95% CI -0.49 to 0.13; P value = 0.26)
Banaszewska 2007	DHEAS (µ/ml)	-1.01 (0.98)	-0.96 (0.90)	-0.05 (95% CI -0.58 to 0.48; P value = 0.85)
Banaszewska 2007	SHBG (nmol/L)	64.5 (37.99)	78.30 (33.92)	-13.80 (95% CI -34.18 to 6.58; P value = 0.18)

Analysis 37.1. Comparison 37 Metformin 850 mg b.i.d. versus metformin 850 mg b.i.d. + simvastatin 20 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin group (standard deviation) N = 33**	**Mean change from baseline in metformin + simvastatin group (standard deviation) N = 36**	**Mean difference (95% CI; P value)**
Banaszewska 2011	Total testosterone (ng/ml)	-0.15 (0.23)	-0.16 (0.18)	0.01 (95% CI -0.09 to 0.11; P value = 0.84)
Banaszewska 2011	Free testosterone (ng/dl)	-0.30 (0.46)	-0.27 (0.48)	-0.03 (95% CI -0.25 to 0.19; P value = 0.79)
Banaszewska 2011	DHEAS (µmol/ml)	0.54 (2.13)	0.59 (1.86)	-0.05 (95% CI -1.00 to 0.90; P value = 0.92)
Banaszewska 2011	SHBG (nmol/L)	2.27 (13.04)	0.43 (10.68)	1.84 (95% CI -3.81 to 7.49; P value = 0.52)

Analysis 38.1. Comparison 38 Simvastatin 20 mg once a day versus metformin 850 mg b.i.d. + simvastatin 20 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in simvastatin group (standard deviation) N = 28**	**Mean change from baseline in metformin + simvastatin group (standard deviation) N = 36**	**Mean difference (95% CI; P value)**
Banaszewska 2011	Total testosterone (ng/ml)	-0.22 (0.16)	-0.16 (0.18)	-0.06 (95% CI -0.14 to 0.02; P value = 0.69)
Banaszewska 2011	Free testosterone (ng/dl)	-0.28 (0.32)	-0.27 (0.48)	-0.01 (95% CI -0.21 to 0.19; P value = 0.92)
Banaszewska 2011	DHEAS (µmol/ml)	-1.64 (2.28)	0.59 (1.86)	-2.23 (95% CI -3.29 to -1.19; P < 0.001)
Banaszewska 2011	SHBG (nmol/L)	-5.19 (11.64)	0.43 (10.68)	-5.62 (95% CI -11.16 to -0.07; P value = 0.05)

Analysis 39.1. Comparison 39 Metformin 850 mg b.i.d. + flutamide 250 mg b.i.d. versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin + flutamide group (standard deviation) N = 20**	**Mean change from baseline in placebo group (standard deviation) N = 19**	**Mean difference (95% CI; P value)**
Gambineri 2006	Total testosterone (nmol/L)	-0.24 (0.12)	-0.15 (0.18)	-0.09 (95% CI -0.19 to 0.01; P value = 0.07)
Gambineri 2006	Androstenedione (nmol/L)	-31.00 (82.63)	-62.00 (73.29)	31.00 (95% CI -17.96 to 79.96; P value = 0.21)
Gambineri 2006	DHEAS (μmol/ml)	-1.10 (0.90)	0.40 (0.72)	-1.50 (95% CI -2.01 to -0.99; P value < 0.001)
Gambineri 2006	SHBG (nmol/L)	3.80 (7.85)	1.50 (11.02)	2.30 (95% CI -3.73 to 8.3; P value = 0.45)

Analysis 40.1. Comparison 40 Metformin 1275 mg to 1700 mg per day + flutamide 250 mg to 500 mg per day versus flutamide 250 mg to 500 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin + flutamide group (standard deviation) N = 20 Gambineri 2006; N = 13 Ibáñez 2002**	**Mean change from baseline in flutamide group (standard deviation) N = 17 Gambineri 2006; N = 10 Ibáñez 2002**	**Mean difference (95% CI; P value)**
Gambineri 2006	Total testosterone (nmol/L)	-0.24 (0.12)	-0.22 (0.14)	-0.02 (95% CI -0.10 to 0.06; P value = 0.64)
Gambineri 2006	Androstenedione (nmol/L)	-31.00 (82.63)	-161.00 (100.24)	130.00 (95% CI 70.15 to 189.95; P value < 0.001)
Gambineri 2006	DHEAS (μmol/ml)	-1.10 (0.90)	-1.40 (0.94)	0.30 (95% CI -0.30 to 0.90; P value = 0.32)
Gambineri 2006	SHBG (nmol/L)	3.80 (7.85)	3.00 (6.79)	0.80 (95% CI -3.92 to 5.52; P value = 0.74)
Ibáñez 2002	Testosterone (ng/dl)	-51.00 (13.29)	-31.00 (27.02)	-20.00 (95% CI -38.24 to -1.76; P value = 0.03)
Ibáñez 2002	SHBG (μg/dl)	0.50 (0.23)	0.30 (0.20)	0.20 (95% CI 0.02 to 0.38; P value = 0.03)
Ibáñez 2002	Androstenedione (ng/dl)	-147.00 (66.13)	-40.00 (42.63)	-107.00 (95% CI -151.61 to -62.39; P value < 0.001)
Ibáñez 2002	DHEAS (μg/dl)	-128.00 (43.86)	-4.00 (28.63)	-124.00 (95% -153.72 to -94.28; P value < 0.001)

Analysis 41.1. Comparison 41 Metformin 1275 mg to 1700 mg per day + flutamide 250 mg to 500 mg per day versus metformin 1275 mg to 1700 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin + flutamide group (standard deviation) N =20 Gambineri 2006; N = 13 Ibáñez 2002**	**Mean change from baseline in metformin group (standard deviation) N = 17 Gambineri 2006; N = 8 Ibáñez 2002**	**Mean difference (95% CI; P value)**
Gambineri 2006	Total testosterone (nmol/L)	-0.24 (0.12)	-0.15 (0.22)	-0.09 (95% CI -0.20 to 0.02; P value = 0.11)

Changes in androgen levels (*Continued*)

Gambineri 2006	Androstenedione (nmol/L)	-31.00 (82.63)	-51 (103.72)	20.00 (95% CI -38.12 to 78.12; P value = 0.50)
Gambineri 2006	DHEAS (μmol/ml)	-1.10 (0.90)	0.10 (0.36)	-1.20 (95% CI -1.62 to -0.78; P value < 0.001)
Gambineri 2006	SHBG (nmol/L)	3.80 (7.85)	2.20 (7.69)	1.6 (95% CI -3.22 to 6.42; P value = 0.51)
Ibáñez 2002	Testosterone (ng/dl)	-51.00 (13.29)	-67.00 (35.97)	16.00 (95% CI -9.95 to 41.95; P value = 0.23)
Ibáñez 2002	SHBG (µg/dl)	0.50 (0.23)	0.40 (0.18)	0.10 (95% CI -0.08 to 0.28; P value = 0.27)
Ibáñez 2002	Androstenedione (ng/dl)	-147.00 (66.13)	-42.00 (48.13)	-105 (95% CI -154.04 to -55.96; P value < 0.001)
Ibáñez 2002	DHEAS (µg/dl)	-128.00 (43.86)	-44.00 (52.66)	-84.00 (95% CI -127.59 to -40.41; P value = 0.0002)

Analysis 42.1. Comparison 42 Finasteride 5 mg once a day versus cyproterone acetate 25 mg once a day + ethinyl estradiol 20 μg 21 days of the month, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride group (standard deviation) N = 20 Beigi 2004; N = 14 Fruzzetti 1999**	**Mean change from baseline in CPA + ethinyl estradiol group N = 20 Beigi 2004; N = 13 Fruzzetti 1999**	**Mean difference (95% CI; P value)**
Beigi 2004	Total testosterone (ng/dl)	38 (27.17)	-66 (27.29)	104 (95% CI 87.12 to 120.88; P value < 0.001)
Beigi 2004	Free testosterone (pg/ml)	0.3 (0.63)	-3.15 (0.85)	3.45 (95% CI 2.99 to 3.91; P value < 0.001)
Beigi 2004	Androstenedione (ng/ml)	0.20 (0.55)	-2.90 (0.58)	3.10 (95% CI 2.75 to 3.45; P value < 0.001)
Beigi 2004	DHEAS (µg/dl)	-2.10 (75.99)	-108.70 (48.19)	106.60 (95% CI 67.16 to 146.04; P value < 0.001)
Beigi 2004	Dihydrotestosterone (ng/dl)	-29.80 (10.81)	-22.80 (7.86)	-7.00 (95% CI -12.86 to -1.14; P value = 0.02)

Changes in androgen levels (*Continued*)

Beigi 2004	SHBG (nmol/L)	1.80 (24.96)	31.60 (27.19)	-29.80 (95% CI -45.98 to -13.62; P value = 0.0003)
Fruzzetti 1999	Testosterone (ng/ml)	0.30 (0.32)	-0.57 (0.37)	0.87 (95% CI 0.61 to 1.13; P value < 0.001)
Fruzzetti 1999	Free testosterone (ng/ml)	0.87 (1.15)	-4.21 (1.58)	5.08 (95% CI 4.03 to 6.13; P value < 0.001)
Fruzzetti 1999	Dihydrotestosterone (ng/ml)	-0.39 (0.67)	-0.25 (0.13)	-0.14 (95% CI -0.50 to 0.22; P value 0.44)
Fruzzetti 1999	Androstenedione (ng/ml)	Unchanged (no further data)	-2.70 (0.98)	Cannot be calculated
Fruzzetti 1999	DHEAS (µg/ml)	Unchanged (no further data)	-0.57 (1.09)	Cannot be calculated
Fruzzetti 1999	SHBG (ng/ml)	Unchanged (no further data)	32 (29.75)	Cannot be calculated

Analysis 43.1. Comparison 43 Flutamide 250 mg b.i.d. versus cyproterone acetate 25 mg once a day + ethinyl estradiol 20 μg 21 days of the month, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide group (standard deviation) N = 15**	**Mean change from baseline in CPA + ethinyl estradiol group (standard deviation) N = 13**	**Mean difference (95% CI; P value)**
Fruzzetti 1999	Testosterone (ng/ml)	Unchanged (no further data)	-0.57 (0.37)	Cannot be calculated
Fruzzetti 1999	Free testosterone (ng/ml)	-0.25 (1.27)	-4.21 (1.58)	3.96 (95% CI 2.89 to 5.03; P value < 0.001)
Fruzzetti 1999	Dihydrotestosterone (ng/ml)	Unchanged (no further data)	-0.25 (0.13)	Cannot be calculated
Fruzzetti 1999	Androstenedione (ng/ml)	Unchanged (no further data)	-2.70 (0.98)	Cannot be calculated
Fruzzetti 1999	DHEAS (µg/ml)	-0.38 (0.39)	-0.57 (1.09)	0.19 (95% CI -0.43 to 0.81; P value = 0.55)

Changes in androgen levels (*Continued*)

Fruzzetti 1999	SHBG (ng/ml)	-1.81 (3.04)	32 (29.75)	-33.81 (95% CI -50.05 to -17.57; P value < 0.001)

Analysis 44.1. Comparison 44 Flutamide 125 mg per day + triphasic OCP versus placebo + tricyclic OCP, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide + OCP group (standard deviation) N = 25**	**Mean change from baseline in placebo + OCP group (standard deviation) N = 31**	**Mean difference (95% CI; P value)**
Calaf 2007	Testosterone (nmol/L)	-0.16 (0.69)	-0.51 (0.55)	0.35 (95% CI 0.02 to 0.68; P value = 0.04)
Calaf 2007	SHBG (nmol/L)	109.10 (42.43)	37.60 (31.34)	71.50 (95% CI 51.54 to 91.46; P value < 0.001)
Calaf 2007	Free Androgen Index	-4.62 (4.71)	-2.20 (2.40)	-2.42 (95% CI -4.45 to -0.39; P value = 0.02)
Calaf 2007	DHEAS (nmol/L)	-2.59 (1.80)	-1.07 (1.61)	-1.52 (95% CI -2.43 to -0.61; P value = 0.001)
Calaf 2007	Androstenedione (nmol/L)	-3.70 (4.20)	-1.99 (2.32)	-1.71 (95% CI -3.55 to 0.1; P value = 0.07)

Analysis 45.1. Comparison 45 Flutamide 250 mg per day + triphasic OCP versus placebo + tricyclic OCP, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide + OCP group (standard deviation) N = 29**	**Mean change from baseline in placebo + OCP group (standard deviation) N = 31**	**Mean difference (95% CI; P value)**
Calaf 2007	Testosterone (nmol/L)	-0.59 (0.74)	-0.51 (0.55)	-0.08 (95% CI -0.41 to 0.25; P = 0.64)
Calaf 2007	SHBG (nmol/L)	104.30 (85.51)	37.60 (31.34)	66.70 (95% CI 33.68 to 99.72; P value < 0.001)
Calaf 2007	Free Androgen Index	-5.41 (3.34)	-2.20 (2.40)	-3.21 (95% CI -4.69 to -1.73; P value < 0.001)

Changes in androgen levels (*Continued*)

Calaf 2007	DHEAS (nmol/L)	-3.53 (2.13)	-1.07 (1.61)	-2.46 (95% CI -3.42 to -1. 50; P value < 0.001)
Calaf 2007	Androstenedione (nmol/L)	-3.67 (2.33)	-1.99 (2.32)	-1.68 (95% CI -2.86 to -0. 50; P value = 0.005)

Analysis 46.1. Comparison 46 Flutamide 375 mg per day + triphasic OCP versus placebo + tricyclic OCP, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide + OCP group (standard deviation) N = 34**	**Mean change from baseline in placebo + OCP group (standard deviation) N = 35**	**Mean difference (95% CI; P value)**
Calaf 2007	Testosterone (nmol/L)	-0.18 (0.48)	-0.51 (0.55)	0.33 (95% CI 0.08 to 0.58; P value = 0.01)
Calaf 2007	SHBG (nmol/L)	129.40 (71.23)	37.60 (31.34)	91.80 (95% CI 65.44 to 118.16; P value < 0.001)
Calaf 2007	Free Androgen Index	-4.72 (2.57)	-2.20 (2.40)	-2.52 (95% CI -3.73 to -1. 31; P value < 0.001)
Calaf 2007	DHEAS (nmol/L)	-3.10 (1.48	-1.07 (1.61)	-2.03 (95% CI -2.78 to -1. 28; P value < 0.001)
Calaf 2007	Androstenedione (nmol/L)	-1.90 (2.70)	-1.99 (2.32)	0.09 (95% CI -1.13 to 1.31; P value = 0.89)

Analysis 47.1. Comparison 47 Flutamide 125 mg per day + triphasic OCP versus flutamide 375 mg per day + triphasic OCP, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in flutamide 125 mg + OCP group (standard deviation) N = 25**	**Mean change from baseline in flutamide 375 mg + OCP group (standard deviation) N = 34**	**Mean difference (95% CI; P value)**
Calaf 2007	Testosterone (nmol/L)	-0.16 (0.69)	-0.18 (0.48)	0.02 (95% CI -0.29 to 0.33; P value = 0.90)
Calaf 2007	SHBG (nmol/L)	109.10 (42.43)	129.40 (71.23)	-20.30 (95% CI -49.45 to 8.85; P value = 0.17)

Changes in androgen levels (*Continued*)

Calaf 2007	Free Androgen Index	-4.62 (4.71)	-4.72 (2.57)	0.10 (95% CI -1.94 to 2.14; P value = 0.92)
Calaf 2007	DHEAS (nmol/L)	-2.59 (1.80)	-3.10 (1.48	0.51 (95% CI -0.35 to 1.37; P value = 0.25)
Calaf 2007	Androstenedione (nmol/L)	-3.70 (4.20)	-1.90 (2.70)	-0.60 (95% CI -2.48 to 1. 28; P value = 0.53)

Analysis 48.1. Comparison 48 GnRH-A 3.75 mg im every 28 days versus GnRH-A 3.75 mg im every 28 days + oestrogen 0.625 mg and medroxyprogesterone 10 mg both on day 1 to 21, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 10**	**Mean change from baseline in GnRH-A + oestrogen + progesterone group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
Carmina 1994	Total testosterone (nmol/ L)	-1.53 (1.00)	-2.04 (0.66)	0.51 (95% CI -0.21 to 1. 23; P value = 0.17)
Carmina 1994	Free testosterone (pmol/L)	-11.20 (7.65)	-14.2 (7.33)	3.00 (95% CI -3.30 to 9. 30; P value = 0.35)
Carmina 1994	Androstenedione (nmol/L)	-6.40 (2.80)	-8.70 (2.19)	2.30 (95% CI 0.17 to 4.43; P value = 0.03)
Carmina 1994	DHEAS (µmol/L)	0.3 (3.16)	-1.60 (2.41)	1.90 (95% CI -0.49 to 4. 29; P value = 0.12)

Analysis 49.1. Comparison 49 GnRH-A 3.6 mg sc every 28 days versus GnRH-A 3.6 mg sc every 28 days + estradiol valerate 2 mg days 5 to 25 + medroxyprogesterone days 16 to 25, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 8**	**Mean change from baseline in GnRH-A group + oestrogen-progestogen replacement (standard deviation) N = 6**	**Mean difference (95% CI; P value)**
Tiitinen 1994	SHBG (nmol/L)	-6 (6.96)	7 (12.66)	-13.00 (95% CI -24.22 to -1.78; P value = 0.02)

Changes in androgen levels (*Continued*)

Tiitinen 1994	Testosterone (nmol/L)	0.08 (0.55)	0.01 (0.68)	0.07 (95% CI 0.59 to 0.73; P value = 0.84)
Tiitinen 1994	Free testosterone (pmol/L)	2.90 (8.08)	-4.60 (15.81)	7.50 (95% CI -6.33 to 21. 33; P value = 0.29)
Tiitinen 1994	Androstenedione (nmol/L)	-0.30 (2.21)	0.30 (2.10)	-0.60 (95% CI -2.87 to 1. 67; P value = 0.60)
Tiitinen 1994	DHEAS (µmol/L)	-1.20 (2.17)	-1.90 (4.08)	0.70 (95% CI -2.89 to 4. 29; P value = 0.70)

Analysis 50.1. Comparison 50 GnRH-A 3.6 mg + OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 0.35 µg + cyproterone acetate 2 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 15**	**Mean change from baseline in OCP group (standard deviation) N = 14**	**Mean difference (95% CI; P value)**
Vegetti 1996	SHBG (nmol/L)	147.95 (73.02)	137.61 (64.79)	10.34 (95% CI -39.83 to 60.51; P value = 0.69)
Vegetti 1996	DHEAS (µg/ml)	-0.27 (0.52)	-0.23 (0.45)	-0.04 (95% CI -0.39 to 0. 31; P value = 0.82)
Vegetti 1996	Free testosterone (pg/ml)	-1.23 (0.82)	-1.09 (1.05)	-0.14 (95% CI -0.83 to 0. 55; P value = 0.69)
Vegetti 1996	Dihydrotestosterone (pg/ml)	0.10 (0.06)	0 (0.10)	0.10 (95% CI 0.04 to 0.16; P value = 0.001)

Analysis 51.1. Comparison 51 GnRH-A 3.75 im every 28 days + OCP (ethinyl estradiol 35 µg + norethindrone 1 mg) versus GnRH-A 3.75 im every 28 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 11**	**Mean change from baseline line in GnRH-A group (standard deviation) N = 11**	**Mean difference (95% CI; P value)**
Carr 1995	Testosterone (nmol/L)	-1.80 (1.05)	-1.20 (0.89)	-0.60 (95% CI -1.41 to 0. 21; P value = 0.15)

Changes in androgen levels (*Continued*)

Carr 1995	Free testosterone (pmol/L)	-12.60 (10.80)	-7.3 (5.82)	-5.30 (95% CI -12.55 to 1. 95; P value = 0.15)
Carr 1995	Androstenedione (nmol/L)	-8.00 (7.45)	-2.00 (1.40)	-6.00 (95% CI -10.48 to -1. 52; P value = 0.009)
Carr 1995	DHEAS (μmol/L)	-0.10 (1.26)	-2.60 (4.97)	2.50 (95% CI -0.53 to 5.53; P value = 0.11)

Analysis 52.1. Comparison 52 GnRH-A 3.75 im every 28 days + OCP (ethinyl estradiol 35 μg + norethindrone 1 mg) versus OCP (ethinyl estradiol 35 μg + norethindrone 1 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 11**	**Mean change from baseline line in OCP group (standard deviation) N = 11**	**Mean difference (95% CI; P value)**
Carr 1995	Testosterone (nmol/L)	-1.80 (1.05)	-1.70 (1.08)	-0.10 (95% CI -0.99 to 0. 79; P value = 0.83)
Carr 1995	Free testosterone (pmol/L)	-12.60 (10.80)	-12.80 (6.85)	0.20 (95% CI -7.36 to 7.76; P value = 0.96)
Carr 1995	Androstenedione (nmol/L)	-8.00 (7.45)	-2.30 (1.41)	-5.70 (95% CI -10.18 to -1. 22; P value = 0.01)
Carr 1995	DHEAS (μmol/L)	-0.10 (1.26)	-0.40 (1.60)	0.30 (95% CI -0.90 to 1.50; P value = 0.63).

Analysis 53.1. Comparison 53 GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus GnRH-A 3.75 mg im every 28 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 12**	**Mean change from baseline in GnRH-A group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
De Leo 2000	SHBG (nmol/L)	42 (13.42)	-14 (7.21)	56.00 (95% CI 47.38 to 64. 62; P value < 0.001)

Changes in androgen levels (*Continued*)

De Leo 2000	Androstenedione (nmol/L)	-6.00 (1.34)	-5.40 (1.34)	-0.60 (95% CI -1.67 to 0.47; P value = 0.27)
De Leo 2000	DHEAS (µmol/L)	-4.70 (1.20)	-3.20 (1.22)	-1.50 (95% CI -2.47 to -0.53; P value = 0.002)
De Leo 2000	Testosterone (nmol/L)	-2.10 (0.59)	-1.60 (0.75)	-0.50 (95% CI -1.04 to 0.04; P value = 0.07)
De Leo 2000	Free testosterone (pmol/L)	-24 (3.16)	-19 (3.16)	-5.00 (95% CI -7.53 to -2.47; P value = 0.0001)

Analysis 54.1. Comparison 54 GnRH-A 3.75 mg im every 28 days + flutamide 250 mg per day versus GnRH-A 3.75 mg im every 28 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + flutamide group (standard deviation) N = 11**	**Mean change from baseline in GnRH-A group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
De Leo 2000	SHBG (nmol/L)	-13 (6.00)	-14 (7.21)	1.00 (95% CI -4.40 to 6.40; P value = 0.72)
De Leo 2000	Androstenedione (nmol/L)	-6.60 (1.34)	-5.40 (1.34)	-1.20 (95% CI -2.30 to -0.10; P value = 0.03)
De Leo 2000	DHEAS (µmol/L)	-6.60 (1.22)	-3.20 (1.22)	-3.40 (95% CI -4.40 to -2.40; P < 0.001)
De Leo 2000	Testosterone (nmol/L)	-2.30 (0.85)	-1.60 (0.75)	-0.70 (95% CI -1.36 to -0.04; P value = 0.04)
De Leo 2000	Free testosterone (pmol/L)	-24 (3.16)	-19 (3.16)	-5.00 (95% CI -7.59 to -2.41; P value = 0.0002)

Analysis 55.1. Comparison 55 GnRH-A 3.75 mg im every 28 days + flutamide 250 mg per day versus GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + flutamide group (standard deviation) N = 11**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
De Leo 2000	SHBG (nmol/L)	-13 (6.00)	42 (13.42)	-55 (95% CI -63.38 to -46.62; P value < 0.001)
De Leo 2000	Androstenedione (nmol/L)	-6.60 (1.34)	-6.00 (1.34)	-0.60 (95% CI -1.70 to 0.50; P value = 0.28)
De Leo 2000	DHEAS (μmol/L)	-6.60 (1.22)	-4.70 (1.20)	-1.90 (95% CI -2.89 to -0.91; P value = 0.0002)
De Leo 2000	Testosterone (nmol/L)	-2.30 (0.85)	-2.10 (0.59)	-0.20 (95% CI -0.80 to 0.40; P value = 0.52)
De Leo 2000	Free testosterone (pmol/L)	-24 (3.16)	-24 (3.16)	0 (95% CI -2.59 to 2.59; P value = 1.00)

Analysis 56.1. Comparison 56 GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 μg + norethindrone 0.4 mg) versus GnRH-A 3.75 mg im every 28 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 11**	**Mean change from baseline in GnRH-A group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
Elkind-Hirsch 1995	Testosterone (ng/dl)	-65.80 (14.98)	-53.50 (14.47)	-12.30 (95% CI -24.36 to -0.24; P value = 0.05)
Elkind-Hirsch 1995	Free testosterone (ng/dl)	-2.70 (1.60)	-2.10 (0.83)	-0.60 (95% CI -1.66 to 0.46; P value = 0.27)
Elkind-Hirsch 1995	SHBG (nmol/L)	110 (67.46)	0 (23.70)	110 (95% CI 67.94 to 152.06; P value < 0.001)
Elkind-Hirsch 1995	DHEAS (μg/dl)	Authors state "no significant difference"	Authors state "no significant difference"	cannot be calculated

Analysis 57.1. Comparison 57 GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg) versus OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 11**	**Mean change from baseline in OCP group (standard deviation) N = 10**	**Mean difference (95% CI; P value)**
Elkind-Hirsch 1995	Testosterone (ng/dl)	-65.80 (14.98)	-29.40 (8.59)	-36.40 (95% CI -46.73 to -26.07; P value < 0.001)
Elkind-Hirsch 1995	Free testosterone (ng/dl)	-2.70 (1.60)	-1.30 (0.87)	-1.40 (95% CI -2.49 to -0.31; P value = 0.01)
Elkind-Hirsch 1995	SHBG (nmol/L)	110 (67.46)	116 (87.50)	-6.00 (95% CI -73.31 to 61.31; P value = 0.86)
Elkind-Hirsch 1995	DHEAS (µg/dl)	Authors state "no significant difference"	Authors state "no significant difference"	Cannot be calculated

Analysis 58.1. Comparison 58 GnRH-A 3.75 mg im every 28 days + OCP (ethinyl estradiol 0.35 µg + cyproterone acetate 2 mg) versus GnRH-A 3.75 mg im every 28 days, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A + OCP group (standard deviation) N = 16 Falsetti 1994; N = 13 Falsetti 1994B**	**Mean change from baseline in GnRH-A group (standard deviation) N = 16 Falsetti 1994; N = 12 Falsetti 1994B**	**Mean difference (95% CI; P value)**
Falsetti 1992	Androstenedione (units not provided)	-54.5% (no standard deviation provided)	-47.5% (no standard deviation provided)	Cannot be calculated
Falsetti 1992	Testosterone (units not provided)	-59.5% (no standard deviation provided)	-48.5% (no standard deviation provided)	Cannot be calculated
Falsetti 1992	Free testosterone (units not provided)	-69.5% (no standard deviation provided)	-61% (no standard deviation provided)	Cannot be calculated
Falsetti 1992	DHEAS (units not provided)	23.5% (no standard deviation provided)	-12.5% (no standard deviation provided)	Cannot be calculated
Falsetti 1992	SHBG (units not provided)	-26% (no standard deviation provided)	150% (no standard deviation provided)	Cannot be calculated

Changes in androgen levels (*Continued*)

Falsetti 1994	Testosterone (ng/ml)	-0.50 (0.26)	-0.45 (0.24)	-0.05 (95% CI -0.22 to 0.12; P value = 0.57)
Falsetti 1994	Androstenedione (ng/ml)	-1.55 (0.46)	-1.45 (0.29)	-0.10 (95% CI -0.37 to 0.17; P value = 0.46)
Falsetti 1994	Free testosterone (pg/ml)	-2.55 (1.51)	-2.25 (1.46)	-0.30 (95% CI -1.33 to 0.73; P value = 0.57)
Falsetti 1994	DHEAS (µg/ml)	-0.65 (0.72)	-0.25 (0.71)	-0.40 (95% CI -0.90 to 0.10; P value = 0.11)
Falsetti 1994	SHBG (nmol/L)	115 (31.21)	3.5 (4.71)	111.50 (95% CI 96.03 to 126.97; P value < 0.001)
Falsetti 1994B	Androstenedione (ng/ml)	-2.30 (0.19)	-2.0 (0.27)	-0.303 (95% CI -0.48 to -0.12; P value = 0.001)
Falsetti 1994B	Testosterone (ng/ml)	-0.90 (0.27)	-0.70 (0.19)	-0.20 (95% CI -0.38 to -0.02; P value = 0.03)
Falsetti 1994B	Free testosterone (pg/ml)	-3.70 (0.63)	-3.10 (0.37)	-0.60 (95% CI -1.00 to -0.20; P value = 0.003)
Falsetti 1994B	DHEAS (µg/ml)	-0.60 (0.19)	-0.50 (0.30)	-0.10 (95% CI -0.30 to 0.10; P value = 0.32)
Falsetti 1994B	SHBG (nmol/L)	102 (22.49)	3.00 (4.94)	99.00 (95% CI 86.46 to 111.54; P value < 0.001)

Analysis 59.1. Comparison 59 GnRH-A 3.75 im every 28 days + conjugated oestrogen 0.625 mg + medroxyprogesterone acetate 10 mg day 1 to 12 versus OCP (ethinyl estradiol 35 µg + ethynodiol diacetate 1 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 9**	**Mean change from baseline in OCP group (standard deviation) N = 8**	**Mean difference (95% CI; P value)**
Azziz 1995	Testosterone (nmol/L)	-0.5 (0.25)	0 (0.34)	-0.50 (95% CI -0.79 to -0.21; P value = 0.0006)
Azziz 1995	Androstenedione (nmol/L)	-2.60 (1.5)	0.1 (3.9)	-2.70 (95% CI -5.57 to 0.17; P value = 0.07)

Changes in androgen levels (*Continued*)

Azziz 1995	SHBG (nmol/L)	20 (25.30)	100 (96.04)	-80.00 (95% CI -148.57 to -11.43; P value = 0.02)

Analysis 60.1. Comparison 60 OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + metformin 500 b.i.d. versus OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change in OCP + metformin group (standard deviation) N = 20**	**Mean change in OCP group (standard deviation) N = 20**	**Mean difference (95% CI; P value)**
Elter 2002	Testosterone (nmol/L)	-1.13 (0.98)	-1.13 (0.97)	0.00 (95% CI -0.60 to 0.60; P value = 1.00)
Elter 2002	Free testosterone (pg/ml)	-4.99 (1.95)	-4.11 (2.80)	-0.88 (95% CI -2.38 to 0. 62; P value = 0.25)
Elter 2002	Androstenedione (nmol/L)	-7.31 (2.66)	-4.81 (1.73)	-2.50 (95% CI -3.89 to -1. 11; P value = 0.0004)
Elter 2002	DHEAS (µmol/L)	0.84 (1.65)	0.11 (1.95)	0.73 (95% CI -0.39 to 1.85; P value = 0.20)
Elter 2002	SHBG (nmol/L)	59.71 (20)	31.83 (14.20)	27.88 (95% CI 17.13 to 38. 63; P value < 0.001)

Analysis 61.1. Comparison 61 OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + metformin 500 mg three times a day versus OCP (ethinyl estradiol 20 μg + drospirenone 3 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + metformin group (standard deviation) N = 15**	**Mean change from baseline in OCP group (standard deviation) N = 16**	**Mean difference (95% CI; P value)**
Fruzzetti 2010	Total testosterone (ng/ml)	-0.06 (0.13)	-0.17 (0.19)	0.11 (95% CI -0.00 to 0. 22; P value = 0.06)
Fruzzetti 2010	SHBG (ng/ml)	6.28 (6.89)	7.07 (7.78)	-0.79 (95% CI -5.96 to 4. 38; P value = 0.76)
Fruzzetti 2010	Androstenedione (ng/ml)	-0.29 (0.57)	-0.39 (0.76)	0.10 (95% CI -0.37 to 0. 57; P value = 0.68)

Analysis 62.1. Comparison 62 OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) versus OCP (drospirenone 3 mg + ethinyl estradiol 20 μg) + cyproterone acetate 12.5 mg (first 10 days of pill strip), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 16**	**Mean change from baseline in OCP + CPA group (standard deviation) N = 16**	**Mean difference (95% CI; P value)**
Fruzzetti 2010	Total testosterone (ng/ml)	-0.17 (0.19)	-0.17 (0.19)	0.0 (95% CI -0.13 to 0.13; P value = 1.00)
Fruzzetti 2010	SHBG (ng/ml)	7.07 (7.78)	5.94 (6.51)	1.13 (95% CI -3.84 to 6. 10; P value = 0.66)
Fruzzetti 2010	Androstenedione (ng/ml)	-0.39 (0.76)	-0.43 (0.63)	0.04 (95% CI -0.44 to 0. 52; P value = 0.87)

Analysis 63.1. Comparison 63 OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + metformin 500 mg three times a day versus OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + cyproterone acetate 12.5 mg (first 10 days of pill strip), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + metformin group (standard deviation) N = 15**	**Mean change from baseline in OCP + CPA group (standard deviation) N = 16**	**Mean difference (95% CI; P value)**
Fruzzetti 2010	Total testosterone (ng/ml)	-0.06 (0.13)	-0.17 (0.19)	0.11 (95% CI -0.00 to 0. 22; P value = 0.06)
Fruzzetti 2010	SHBG (ng/ml)	6.28 (6.89)	5.94 (6.51)	0.34 (95% CI -4.39 to 5. 07; P value = 0.89)
Fruzzetti 2010	Androstenedione (ng/ml)	-0.29 (0.57)	-0.43 (0.63)	0.14 (95% CI -0.28 to 0. 56; P value = 0.52)

Analysis 64.1. Comparison 64 OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + finasteride 5 mg once a day on day 1 to 14, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 23**	**Mean change from baseline in OCP + finasteride group (standard deviation) N = 23**	**Mean difference (95% CI: P value)**
Tartagni 2000	Free testosterone (pg/ml)	-2.26 (0.90)	-2.76 (0.31)	0.50 (95% CI 0.11 to 0.89; P value = 0.01)
Tartagni 2000	DHEAS (µg/ml)	-1.36 (0.8)	1.52 (0.82)	-2.88 (95% CI -3.35 to -2.41; P value < 0.001)
Tartagni 2000	SHBG (µg/ml)	-0.1 (0.75)	-0.68 (1.07)	0.58 (95% CI 0.05 to 1.11: P value = 0.03)
Tartagni 2000	Androstenedione (ng/ml)	-3.66 (1.39)	-4.34 (1.31)	0.68 (95% CI -0.10 to 1.46; P value = 0.09)

Analysis 65.1. Comparison 65 OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + cyproterone acetate 12.5 mg day 1 to 10 versus OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + spironolactone 100 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + CPA group (standard deviation) N = 13**	**Mean change from baseline in OCP + spironolactone group (standard deviation) N = 15**	**Mean difference (95% CI; P value)**
Lumachi 2003	Testosterone (pmol/L)	-3.5 (2.52)	-1.7 (2.75)	-1.80 (95% CI -3.75 to 0.15; P value = 0.07)
Lumachi 2003	DHEAS (µmol/L)	0.09 (1.62)	-0.27 (1.17)	0.36 (95% CI -0.70 to 1.42; P value = 0.51)
Lumachi 2003	Androstenedione (nmol/L)	-0.72 (1.20)	-0.56 (1.55)	-0.16 (95% CI -1.18 to 0.86; P value = 0.76)

Analysis 66.1. Comparison 66 OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + cyproterone acetate 50 mg once a day on day 1 to 10 versus OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) + spironolactone 100 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in OCP + CPA group (standard deviation) N = 21	Mean change from baseline in OCP + spironolactone group (standard deviation) N = 21	Mean difference (95% CI; P value)4
Erenus 1996	Testosterone (ng/dl)	-12.20 (13.34)	-14.13 (15.32)	1.93 (95% CI -6.76 to 10.62; P value = 0.66)
Erenus 1996	DHEAS (mg/dl)	-63.7 (64.18)	-47.41 (62.06)	-16.29 (95% CI -54.47 to 21.89; P value = 0.40)

Analysis 67.1. Comparison 67 OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + cyproterone acetate 50 mg b.i.d. versus OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + spironolactone 100 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in OCP + CPA group (standard deviation) N = 45	Mean change from baseline in OCP + spironolactone group (standard deviation) N = 44	Mean difference (95% CI; P value)
Kelekci 2012	Total testosterone (ng/ml)	-0.20 (0.12)	-0.23 (0.10)	0.03 (95% CI -0.02 to 0.08; P value = 0.20)
Kelekci 2012	DHEAS (μg/ml)	-55.04 (42.77)	-43.97 (24.64)	-11.07 (95% CI -25.53 to 3.39; P value = 0.13)

Analysis 68.1. Comparison 68 OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + cyproterone acetate 50 mg b.i.d. versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + cyproterone acetate 50 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in OCP (including DRSP) + CPA group (standard deviation) N = 45	Mean change from baseline in OCP (including CPA) + CPA group (standard deviation) N = 45	Mean difference (95% CI; P value)
Kelekci 2012	Total testosterone (ng/ml)	-0.20 (0.12)	-0.13 (0.15)	-0.07 (95% CI -0.13 to -0.01; P value = 0.01)

Changes in androgen levels (*Continued*)

Kelekci 2012	DHEAS (µg/ml)	-55.04 (42.77)	-40.25 (25.39)	-14.79 (95% CI -29.32 to -0.26; P value = 0.05)

Analysis 69.1. Comparison 69 OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) + spironolactone 100 mg once a day versus OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + cyproterone acetate 50 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP (including DRSP) + spironolactone group (standard deviation) N = 44**	**Mean change from baseline in OCP (including CPA) + CPA group (standard deviation) N =45**	**Mean difference (95% CI; P value)**
Kelekci 2012	Total testosterone (ng/ml)	-0.23 (0.10)	-0.13 (0.15)	-0.10 (95% CI -0.15 to -0.05; P value = 0.002)
Kelekci 2012	DHEAS (µg/ml)	-43.97 (24.64)	-40.25 (25.39)	-3.72 (95% CI -14.11 to 6.67; P value = 0.48)

Analysis 70.1. Comparison 70 OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + spironolactone 100 mg once daily versus OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + finasteride 5 mg once daily, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + spironolactone group (standard deviation) N = 55**	**Mean change from baseline in OCP + finasteride group (standard deviation) N = 57**	**Mean difference (95% CI; P value)**
Kriplani 2009	Total testosterone (ng/ml)	-0.50 (0.82)	-0.30 (0.63)	-0.20 (95% CI -0.47 to 0.07; P value = 0.15)
Kriplani 2009	DHEAS (µg/dl)	-44.30 (74.38)	-57.50 (79.88)	13.20 (95% CI -15.37 to 41.77; P value = 0.37)

Analysis 71.1. Comparison 71 OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + spironolactone 100 mg versus OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + finasteride 5 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + spironolactone group (standard deviation) N = 15**	**Mean change from baseline in OCP + finasteride group (standard deviation) N = 13**	**Mean difference (95% CI; P value)**
Lumachi 2003	Testosterone (pmol/L)	-1.7 (2.75)	2.4 (1.49)	-4.10 (95% CI -5.71 to -2.49; P value < 0.001)
Lumachi 2003	DHEAS (μmol/L)	-0.27 (1.17)	0.19 (0.86)	-0.46 (95% CI -1.21 to 0.29; P value = 0.23)
Lumachi 2003	Androstenedione (nmol/L)	-0.56 (1.55)	0.37 (1.52)	-0.93 (95% CI -2.07 to 0.21; P value = 0.11)

Analysis 72.1. Comparison 72 OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + cyproterone acetate 12.5 mg day 1 to 10 versus OCP (ethinyl estradiol 30 μg + gestodene 75 μg) + finasteride 5 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + CPA group (standard deviation) N = 13**	**Mean change from baseline in OCP + finasteride group (standard deviation) N = 13**	**Mean difference (95% CI; P value)**
Lumachi 2003	Testosterone (pmol/L)	-3.5 (2.52)	2.4 (1.49)	-5.90 (95% CI -7.49 to -4.31; P value < 0.001)
Lumachi 2003	DHEAS (μmol/L)	0.09 (1.62)	0.19 (0.86)	-0.10 (95% CI -1.10 to 0.90; P value = 0.84)
Lumachi 2003	Androstenedione (nmol/L)	-0.72 (1.20)	0.37 (1.52)	-1.09 (95% CI -2.14 to -0.04; P value = 0.04)

Analysis 73.1. Comparison 73 OCP (triphasic including ethinyl estradiol and levonorgestrel) + spironolactone 100 mg once a day versus ethinyl estradiol 30 µg day on day 5 to 25 + cyproterone acetate 100 mg once a day on day 5 to 14, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + spironolactone group (standard deviation) N = 20**	**Mean change from baseline in EE + CPA group (standard deviation) = 26**	**Mean difference (95% CI; P value)**
O'Brien 1991	Testosterone (nmol/L)	-0.60 (0.61)	-1.00 (0.70)	0.40 (95% CI 0.02 to 0.78; P value = 0.04)
O'Brien 1991	DHEAS (µmol/L)	-0.10 (2.32)	-1.90 (2.19)	1.80 (95% CI 0.48 to 3.12; P value = 0.008)
O'Brien 1991	Androstenedione (nmol/L)	-1.10 (3.46)	-2.40 (1.92)	1.30 (95% CI -0.39 to 2.99; P value = 0.13)
O'Brien 1991	SHBG (nmol/L)	51.70 (55.15)	62.40 (42.22)	-10.70 (95% CI -39.81 to 18.41; P value = 0.47)

Analysis 74.1. Comparison 74 OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + sibutramine 10 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 14**	**Mean change from baseline in OCP + sibutramine group (standard deviation) N = 14**	**Mean difference (95% CI; P value)**
Sabuncu 2003	Testosterone (ng/dl)	-44.0 (17.62)	-41.80 (20.58)	-2.20 (95% CI -16.39 to 11.99; P value = 0.76)
Sabuncu 2003	Free testosterone (ng/dl)	-2.20 (0.61)	-2.60 (0.72)	0.40 (95% CI -0.09 to 0.89; P value = 0.11)
Sabuncu 2003	SHBG (nmol/L)	41.30 (31.30)	60.50 (34.63)	-19.20 (95% CI -43.65 to 5.25; P value = 0.12)
Sabuncu 2003	DHEAS (µg/dl)	-59.30 (52.38)	-63.40 (65.44)	4.10 (95% CI -39.81 to 48.01; P value = 0.85)

Analysis 75.1. Comparison 75 OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + sibutramine 10 mg once a day versus sibutramine 10 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP + sibutramine group (standard deviation) N = 14**	**Mean change from baseline in sibutramine group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
Sabuncu 2003	Testosterone (ng/dl)	-41.80 (20.58)	-51.80 (16.58)	10.00 (95% CI -4.29 to 24.29; P value = 0.17)
Sabuncu 2003	Free testosterone (ng/dl)	-2.60 (0.72)	-2.0 (0.61)	-0.60 (95% CI -1.11 to -0.09; P value = 0.02)
Sabuncu 2003	SHBG (nmol/L)	60.50 (34.63)	31.70 (18.63)	28.80 (95% CI -7.82 to 49.78; P value = 0.007)
Sabuncu 2003	DHEAS (μg/dl)	-63.40 (65.44)	-52.70 (51.37)	-10.70 (95% CI -55.64 to 34.24; P value = 0.64)

Analysis 76.1. Comparison 76 OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus pioglitazone 7.5 mg + flutamide 62.5 mg + metformin 850 mg all once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (stand deviation) N = 17**	**Mean change from baseline in combined treatment group (standard deviation) N = 17**	**Mean difference (95% CI; P value)**
Ibáñez 2012	Testosterone (ng/dl)	-27 (24.74)	-22 (24.74)	-5.00 (95% CI -21.63 to 11.63; P value = 0.56)
Ibáñez 2012	SHBG (nmol/l)	139 (32.98)	8 (8.25)	131.00 (95% CI 114.84 to 147.16; P value < 0.001)
Ibáñez 2012	Androstenedione (ng/dl)	-111 (32)	-109 (38)	-2.00 (95% CI -25.62 to 21.62; P value = 0.87)
Ibáñez 2012	DHEAS (μg/dl)	-61 (19)	13 (13)	-74.00 (95% CI -84.94 to -63.06; P value < 0.001)

Analysis 77.1. Comparison 77 Pioglitazone + transdermal contraceptive + metformin + flutamide versus placebo + transdermal contraceptive + metformin + flutamide, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in pioglitazone + combined treatment group (standard deviation) N = 19**	**Mean changes from baseline in placebo + combined treatment group (standard deviation) N = 19**	**Mean difference (95% CI; P value)**
Ibáñez 2009	Testosterone (ng/dl)	-29 (13.78)	-27 (13.07)	-2.00 (95% CI -10.54 to 6.54; P value = 0.65)
Ibáñez 2009	Androstenedione (ng/dl)	-208 (115.82)	-168 (90.70)	-40.00 (95% CI -106.15 to 26.15; P value = 0.24)
Ibáñez 2009	SHBG (nmol/L)	135 (21.53)	132 (21.53)	3.00 (95% CI -10.69 to 16.69; P value = 0.67)
Ibáñez 2009	DHEAS µg/dl)	-91.00 (85.80)	-51.00 (66.68)	-40.00 (95% CI -88.86 to 8.86; P value = 0.11)

Analysis 78.1. Comparison 78 Cyproterone acetate 50 mg per day 20 days per month + ethinyl estradiol 35 µg over the last 10 days of CPA treatment versus spironolactone 200 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in CPA + EE group (standard deviation) N = 23**	**Mean change from baseline in spironolactone group (standard deviation) N = 21**	**Mean difference (95% CI; P value)**
Spritzer 2000	Testosterone (nmol/L)	-1.18 (0.69)	0.2 (0.88)	-1.38 (95% CI -1.85 to -0.91; P value < 0.001)
Spritzer 2000	Androstenedione (nmol/L)	-3.19 (2.27)	2.04 (2.98)	-5.23 (95% CI -6.81 to -3.65; P value < 0.001)

Analysis 79.1. Comparison 79 Dexamethasone 0.37 mg/day versus dexamethasone 0.37 mg/day + spironolactone 100 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in dexamethasone group (standard deviation) N = 12**	**Mean change from baseline in dexamethasone + spironolactone group (standard deviation) N = 30**	**Mean difference (95% CI; P value)**
Carmina 1998	Testosterone (ng/dl)	-60 (10.39)	-64.40 (15.41)	4.40 (95% CI -3.66 to 12.46; P value = 0.28)
Carmina 1998	Free testosterone (pg/ml)	-3.10 (1.09)	-3.48 (1.63)	0.38 (95% CI -0.47 to 1.23; P value = 0.38)
Carmina 1998	DHEAS (µg/ml)	-2.60 (0.84)	-2.62 (1.19)	0.02 (95% CI -0.62 to 0.66; P value = 0.95)

Analysis 80.1. Comparison 80 Spironolactone 100 mg/day versus dexamethasone 0.37 mg/day + spironolactone 100 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in spironolactone group (standard deviation) N = 12 Carmina 1998; N = 10 Prezelj 1989**	**Mean change from baseline in dexamethasone + spironolactone group (standard deviation) N = 30 Carmina 1998; N = 13 Prezelj 1989**	**Mean difference (95% CI; P value)**
Carmina 1998	Testosterone (ng/dl)	-12 (4.56)	-64.40 (15.41)	76.40 (95% CI 70.31 to 82.49; P value < 0.001)
Carmina 1998	Free testosterone (pg/ml)	-0.40 (1.28)	-3.48 (1.63)	3.08 (95% CI 2.15 to 4.01; P value < 0.001)
Carmina 1998	DHEAS (µg/ml)	0.20 (1.09)	-2.62 (1.19)	2.82 (95% CI 2.07 to 3.57; P value < 0.001)
Prezelj 1989	Testosterone (nmol/L)	-0.4 (2.16)	-1.1 (2.53)	0.70 (95% CI -1.22 to 2.62; P value = 0.47)
Prezelj 1989	Androstenedione (nmol/L)	3.4 (7.16)	-4.2 (7.9)	7.60 (95% CI 1.42 to 13.78; P value = 0.02)
Prezelj 1989	DHEAS (µmol/L)	-1.8 (6.7)	-3.9 (7.45)	2.10 (95% CI -3.70 to 7.90; P value = 0.48)

Analysis 81.1. Comparison 81 Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle + metformin 1000 mg b.i.d. versus metformin 1000 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in clomiphene + metformin group (standard deviation) N = 168**	**Mean change from baseline in metformin only group (standard deviation) N = 172**	**Mean difference (95% CI; P value)**
Roth 2012	Testosterone (ng/dl)	-9.1 (33.1)	-7.4 (27.6)	-1.70 (95% CI -8.19 to 4.79; P value = 0.61)
Roth 2012	SHBG (nmol/L)	15.4 (19.5)	2.7 (13.5)	12.70 (95% CI 9.13 to 16.27; P value < 0.001)

Analysis 82.1. Comparison 82 Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle + metformin 1000 mg b.i.d. versus clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in clomiphene + metformin group (standard deviation) N = 168**	**Mean change from baseline in clomiphene only group (standard deviation) N = 165**	**Mean difference (95% CI; P value)**
Roth 2012	Testosterone (ng/dl)	-9.1 (33.1)	-2.6 (31.7)	-6.50 (95% CI -13.46 to 0.46; P value = 0.07)
Roth 2012	SHBG (nmol/L)	15.4 (19.5)	13.4 (16.0)	2.00 (95% CI -1.83 to 5.83; P value = 0.31)

Analysis 83.1. Comparison 83 OCP (ethinyl estradiol 35 μg + norgestimate 0.25 mg) versus metformin 1000 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 15**	**Mean change in metformin group (standard deviation) N = 16**	**Mean difference (95% CI; P value)**
Allen 2005	Testosterone (ng/dl)	-18.0 (5.49)	-18.5 (3.96)	0.50 (95% CI -2.89 to 3.89; P value = 0.77)
Allen 2005	Free testosterone (ng/dl)	-0.9 (0.19)	-0.5 (0.13)	-0.40 (95% CI -0.52 to -0. 28; P value < 0.001)

Analysis 84.1. Comparison 84 OCP ethinyl estradiol 30 μg + desogestrel 0.15 mg) versus metformin 850 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 10**	**Mean change from baseline in metformin group (standard deviation) N = 6**	**Mean difference (95% CI; P value)**
Hoeger 2008	Testosterone (ng/dl)	-28.50 (17.16)	-1.60 (22.12)	-26.90 (95% CI -47.55 to -6.25; P value = 0.01)
Hoeger 2008	SHBG (nmol/L)	75.20 (57.57)	-2.40 (13.37)	77.60 (95% CI 40.35 to 114.85; P value < 0.001)

Analysis 85.1. Comparison 85 OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus metformin 850 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 15**	**Mean change in metformin group (standard deviation) N = 12**	**Mean difference (95% CI; P value)**
Harborne 2003	Testosterone (ng/ml)	-0.84	-0.37	
Harborne 2003	SHBG (nmol/L)	86	-1.6	
Harborne 2003	DHEAS (μmol/L)	-2.8	0.6	
Harborne 2003	Androstenedione (ng/ml)	-3.4	-1.2	
Luque-Ramírez 2007	Free testosterone (ng/dl)	-0.7 (0.37)	-0.2 (0.38)	-0.50 (95% CI -0.79 to -0.21; P value = 0.0006)
Luque-Ramírez 2007	Androstenedione (ng/ml)	-1.3 (0.51)	-0.2 (0.70)	-1.10 (95% CI -1.57 to -0.63; P value < 0.001)
Luque-Ramírez 2007	DHEAS (ng/dl)	-738 (618.71)	250 (580.49)	-988.00 (95% CI -1441.77 to -534.23; P value < 0.001)
Luque-Ramírez 2007				

Analysis 86.1. Comparison 86 OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) versus lifestyle modification, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in OCP group (standard deviation) N = 10	Mean change from baseline in lifestyle modification group (standard deviation) N = 8	Mean difference (95% CI; P value)
Hoeger 2008	Testosterone (ng/dl)	-28.50 (17.16)	0.60 (18.92)	-29.10 995% CI -45.98 to -12.22; P value = 0.0007)
Hoeger 2008	SHBG (nmol/L)	75.20 (57.57)	17.40 (13.86)	57.80 (95% CI 20.85 to 94.75; P value = 0.002)

Analysis 87.1. Comparison 87 OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus sibutramine 10 mg once a day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in OCP group (standard deviation) N = 14	Mean change from baseline in sibutramine group (standard deviation) N = 12	Mean difference (95% CI; P value)
Sabuncu 2003	Testosterone (ng/dl)	-44.0 (17.62)	-51.80 (16.58)	7.80 (95% CI -5.36 to 20.96; P value = 0.25)
Sabuncu 2003	Free testosterone (ng/dl)	-2.20 (0.61)	-2.0 (0.61)	-0.20 (95% CI -0.67 to 0.27; P value = 0.40)
Sabuncu 2003	SHBG (nmol/L)	41.30 (31.30)	31.70 (18.63)	9.60 (95% CI -9.89 to 29.09; P value = 0.33)
Sabuncu 2003	DHEAS (μg/dl)	-59.30 (52.38)	-52.70 (51.37)	-6.60 (95% CI -46.57, to 33.37; P value = 0.75)

Analysis 88.1. Comparison 88 OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus finasteride 5 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in OCP group (standard deviation) N = 21	Mean change from baseline in finasteride group (standard deviation) N = 21	Mean difference (95% CI; P value)
Sahin 1998	Free testosterone (pg/ml)	-1.96 (1.17)	0.31 (1.38)	-2.27 (95% CI -3.04 to -1.50; P value < 0.001)

Changes in androgen levels (*Continued*)

Sahin 1998	DHEAS (µgram/dl)	-45 (68.25)	-7 (98.92)	-38.00 (95% CI -89.40 to 13.40; P value = 0.15)
Sahin 1998	SHBG (nmol/L)	144.25 (85.75)	-1.66 (10.96)	145.91 995% CI 108.94 to 182.88; P value < 0.001)

Analysis 89.1. Comparison 89 OCP (ethinyl estradiol 30 µg + drospirenone 3 mg) versus combined contraceptive vaginal ring (ethinyl estradiol 15 µg + etonogestrel 1.2 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in OCP group (standard deviation) N = 19**	**Mean change from baseline in vaginal contraceptive ring group (standard deviation) N = 18**	**Mean difference (95% CI; P value)**
Battaglia 2010	Androstenedione (nmol/L)	-4.0 (1.97)	-3.10 (1.98)	-0.90 (95% CI -2.17 to 0.37; P value = 0.17)
Battaglia 2010	Testosterone (nmol/L)	-0.60 (0.42)	-0.20 (0.32)	-0.40 (95% CI -0.64 to -0.16; P value = 0.001)
Battaglia 2010	SHBG (nmol/L)	127 (14.75)	108 (24.12)	19.00 (95% CI 6.03 to 31.97; P value = 0.004)

Analysis 90.1. Comparison 90 Finasteride 5 mg versus spironolactone 100 mg, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in finasteride group (standard deviation) N = 10 Moghetti 2000; N = 9 Wong 1995**	**Mean change from baseline in spironolactone group (standard deviation) N = 10 Moghetti 2000; N = 5 Wong 1995**	**Mean difference (95% CI; P value)**
Moghetti 2000	Free testosterone (pg/ml)	0.74 (0.83)	-0.04 (0.59)	0.78 995% CI 0.15 to 1.41; P value = 0.02)
Moghetti 2000	DHEAS (µgram/L)	-301 (358.81)	159 (607.07)	-460.00 (95% CI -897.07 to -22.93; P value = 0.04)
Moghetti 2000	Testosterone (nmol/L)	0.56 (0.34)	-0.02 (0.42)	0.58 (95% CI 0.25 to 0.91; P value = 0.0007)

Changes in androgen levels (*Continued*)

Moghetti 2000	Androstenedione (nmol/L)	1.70 (2.58)	1.20 (4.56)	0.50 (95% CI -2.75, 3.75; P value = 0.76)
Wong 1995	Testosterone (pmol/L)	No change	No significant increase at 6 months	Cannot be calculated
Wong 1995	DHT (pmol/L)	No change	Negligible decrease at 6 months	Cannot be calculated
Wong 1995	Androstenedione (pmol/L)	No change	No significant decrease at 6 months	Cannot be calculated
Wong 1995	DHEAS (nmol/L)	No change	No significant decrease at 6 months	Cannot be calculated

Analysis 91.1. Comparison 91 Flutamide 250 mg once to b.i.d. versus metformin 1275 mg to 1700 mg per day, Outcome 1 Mean change from baseline in Ferriman-Gallwey score.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 91 Flutamide 250 mg once to b.i.d. versus metformin 1275 mg to 1700 mg per day

Outcome: 1 Mean change from baseline in Ferriman-Gallwey score

Study or subgroup	Favours flutamide N	Mean(SD)	Metformin N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Less than 12 month duration of study drug						
Esmaeilzadeh 2010	20	-4.3 (2.43)	20	-2.8 (3.01)		-1.50 [-3.20, 0.20]
Ib ez 2002	10	-6.3 (2.47)	8	-5.6 (2.77)		-0.70 [-3.16, 1.76]
2 12 month duration of study drug						
Gambineri 2006	17	-8.9 (5.53)	20	-2.6 (5.37)		-6.30 [-9.83, -2.77]

Analysis 91.2. Comparison 91 Flutamide 250 mg once to b.i.d. versus metformin 1275 mg to 1700 mg per day, Outcome 2 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in flutamide group (standard deviation) N = 20 Esmaeilzadeh 2010; N = 20 Gambineri 2006; N = 10 Ibáñez 2002	Mean change from baseline in metformin group (standard deviation) N = 20 Esmaeilzadeh 2010; N = 20 Gambineri 2006; N = 8 Ibáñez 2002	Mean difference (95% CI; P value)
Esmaeilzadeh 2010	Total testosterone (nmol/L)	-0.24 (0.44)	-0.32 (0.62)	0.08 (95% CI -0.25 to 0.41; P value = 0.64)
Esmaeilzadeh 2010	Free testosterone (pmol/L)	-0.62 (2.49)	-0.44 (2.04)	-0.18 (95% CI -1.59 to 1.23; P value = 0.80)
Esmaeilzadeh 2010	DHEAS (µmol/L)	-29.08 (143.79)	-2.82 (77.21)	-26.26 (95% CI -97.79 to 45.27; P value = 0.47)
Esmaeilzadeh 2010	SHBG (nmol/L)	5.67 (37.81)	1.65 (16.61)	4.02 (95% CI -14.08 to 22.12; P value = 0.66)
Gambineri 2006	Total testosterone (nmol/L)	-0.22 (0.14)	-0.15 (0.22)	-0.07 (95% CI -0.19 to 0.05; P value = 0.24)
Gambineri 2006	Androstenedione (nmol/L)	-161 (100.24)	-51 (103.72)	-110.00 (95% CI -175.85 to -44.15; P value = 0.001)
Gambineri 2006	DHEAS (μmol/ml)	-1.40 (0.94)	0.10 (0.36)	-1.50 (95% CI -1.97 to -1.03; P value < 0.001)
Gambineri 2006	SHBG (nmol/L)	3.00 (6.79)	2.20 (7.69)	0.80 (95% CI -3.87 to 5.47; P value = 0.74)
Ibáñez 2002	Testosterone (ng/dl)	-31.00 (27.02)	-67.00 (35.97)	36.00 (95% CI 5.97, 66.03; P value = 0.02)
Ibáñez 2002	SHBG (µg/dl)	0.30 (0.20)	0.40 (0.18)	-0.10 (95% CI -0.28, 0.08; P value = 0.27)
Ibáñez 2002	Androstenedione (ng/dl)	-40.00 (42.63)	-42.00 (48.13)	2.00 (95% CI -40.55 to 44.55; P value = 0.93)
Ibáñez 2002	DHEAS (µg/dl)	-4.00 (28.63)	-44.00 (52.66)	40.00 (95% CI -0.58 to 80.58; P value = 0.05)

Analysis 92.1. Comparison 92 Finasteride 5 mg once a day versus flutamide 250 mg once to b.i.d., Outcome 1 Number of adverse events.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 92 Finasteride 5 mg once a day versus flutamide 250 mg once to b.i.d.

Outcome: 1 Number of adverse events

Study or subgroup	Finasteride n/N	Flutamide n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fruzzetti 1999	0/15	0/15			Not estimable
Moghetti 2000	1/5	1/10		56.0 %	2.00 [0.16, 25.75]
Müderris 2000	4/35	0/35		44.0 %	9.00 [0.50, 161.13]
Total (95% CI)	**55**	**60**		**100.0 %**	**3.87 [0.57, 26.24]**

Total events: 5 (Finasteride), 1 (Flutamide)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.65$, df = 1 (P = 0.42); $I^2 = 0.0\%$

Test for overall effect: Z = 1.39 (P = 0.17)

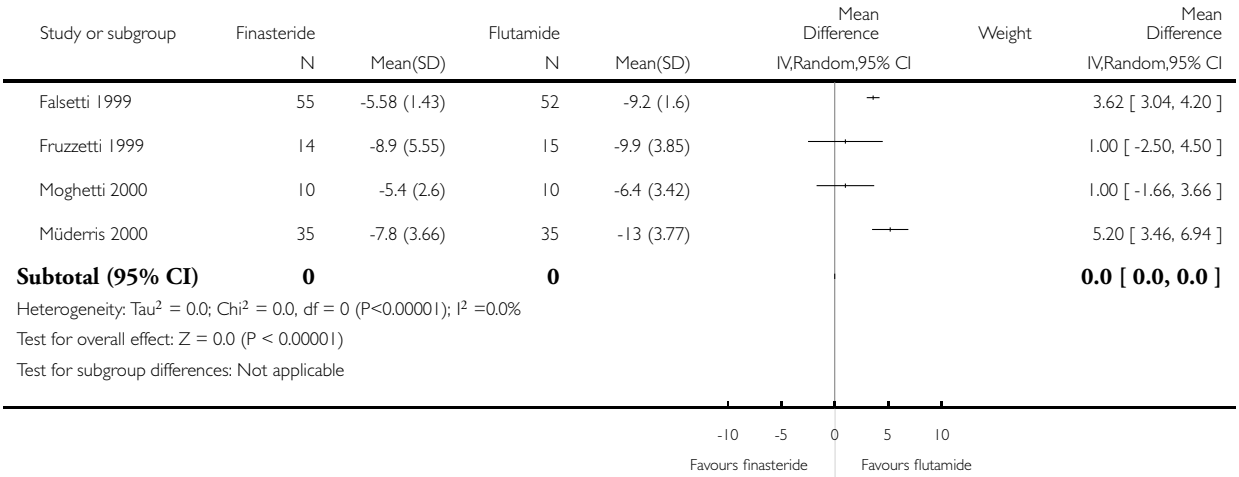
Test for subgroup differences: Not applicable

Analysis 92.2. Comparison 92 Finasteride 5 mg once a day versus flutamide 250 mg once to b.i.d., Outcome 2 Mean change from baseline in Ferriman-Gallwey score.

Review: Interventions for hirsutism (excluding laser and photoepilation therapy alone)

Comparison: 92 Finasteride 5 mg once a day versus flutamide 250 mg once to b.i.d.

Outcome: 2 Mean change from baseline in Ferriman-Gallwey score



Analysis 92.3. Comparison 92 Finasteride 5 mg once a day versus flutamide 250 mg once to b.i.d., Outcome 3 Change in androgen levels.

Change in androgen levels

Study	Androgen	Mean change from baseline in finasteride group (standard deviation) N = 55 Falsetti 1999; N = 14 Fruzzetti 1999; N = 10 Moghetti 2000; N = 35 Müderris 2000	Mean change from baseline in flutamide group (standard deviation) N = 52 Falsetti 1999; N = 15 Fruzzetti 1999; N = 10 Moghetti 2000; N = 35 Müderris 2000	Mean difference (95% CI; P value)
Falsetti 1999	Testosterone (ng/ml)	0.36 (0.13)	-0.04 (0.16)	0.40 (95% CI 0.34 to 0.46; P value < 0.001)
Falsetti 1999	Free testosterone (pg/ml)	0.24 (0.33)	0.02 (0.31)	0.22 (95% CI 0.10 to 0.34; P value = 0.004)
Falsetti 1999	Androstenedione (ng/ml)	0.24 (0.37)	-0.20 (0.33)	0.44 (95% CI 0.31 to 0.57; P value < 0.001)
Falsetti 1999	DHEAS (µg/ml)	-0.14 (0.53)	-0.20 (0.51)	0.06 (95% CI -0.14 to 0.26; P value = 0.55)

Change in androgen levels (*Continued*)

Falsetti 1999	SHBG (nmol/L)	-2.20 (3.79)	-0.67 (4.17)	-1.53 (95% CI -3.04 to -0.02; P value = 0.05)
Falsetti 1999				
Fruzzetti 1999	Testosterone (ng/ml)	0.30 (0.32)	Authors state not significantly changed	Cannot be calculated
Fruzzetti 1999	Free testosterone (ng/ml)	0.87 (1.15)	-0.25 (1.27)	1.12 (95% CI 0.24 to 2.00; P value = 0.01)
Fruzzetti 1999	Androstenedione (ng/ml)	Authors state unchanged	Authors state not significantly changed	Cannot be calculated
Fruzzetti 1999	DHEAS (µgram/ml)	Authors state unchanged	-0.38 (0.39)	Cannot be calculated
Fruzzetti 1999	SHBG (ng/ml)	Authors state unchanged	-1.81 (3.04)	Cannot be calculated
Fruzzetti 1999	Dihydrotestosterone (ng/ml)	-0.39 (0.67)	Authors state not significantly changed	Cannot be calculated
Moghetti 2000	Testosterone (nmol/L)	0.56 (0.34)	-0.05 (0.44)	0.61 (95% CI 0.27 to 0.95; P value = 0.0005)
Moghetti 2000	Free testosterone (pg/ml)	0.74 (0.83)	-0.58 (0.90)	1.32 (95% CI 0.56 to 2.08; P value = 0.0007)
Moghetti 2000	Androstenedione (nmol/L)	1.70 (2.58)	-2.7 (3.36)	4.40 (95% CI 1.77 to 7.03; P value = 0.001)
Moghetti 2000	DHEAS (µgram/L)	-301 (358.81)	-613 (438.41)	312.00 (95% CI -39.13 to 663.13; P value = 0.08)
Moghetti 2000				
Moghetti 2000				
Müderris 2000	Testosterone (ng/dl)	6.00 (23.64)	1.20 (15.63)	4.80 (95% CI -4.59 to 14.19; P value = 0.32)
Müderris 2000	Free testosterone (pg/ml)	-0.50 (1.44)	-0.40 (1.22)	-0.10 (95% CI -0.73 to 0.53; P value = 0.75)
Müderris 2000	Androstenedione (ng/ml)	-0.30 (0.82)	-0.40 (0.57)	0.10 (95% CI -0.23 to 0.43; P value = 0.55)
Müderris 2000	DHEAS (ng/ml)	-53.60 (89.37)	-0.70 (36.89)	-52.90 (95% CI -84.93 to -20.87; P value = 0.001)

Change in androgen levels (*Continued*)

Müderris 2000	SHBG (nmol/L)	8.90 (9.71)	0.70 (6.21)	8.20 (5% CI 4.38 to 12.02; P value < 0.001)
Müderris 2000				

Analysis 93.1. Comparison 93 Metformin 850 mg b.i.d. versus lifestyle modification, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in metformin group (standard deviation) N = 6**	**Mean change from baseline in lifestyle modification group (standard deviation) N = 8**	**Mean difference (95% CI; P value)**
Hoeger 2008	Testosterone (ng/dl)	-1.60 (22.12)	0.60 (18.92)	-2.20 (95% CI -24.23 to 19.83; P value = 0.84)
Hoeger 2008	SHBG (nmol/L)	-2.40 (13.37)	17.40 (13.86)	-19.80 (95% CI -34.18 to -5.42; P value = 0.007)

Analysis 94.1. Comparison 94 GnRH-A 3.75 mg im every 28 days versus OCP (ethinyl estradiol 35 μg + norethindrone 1 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 11**	**Mean change from baseline line in GnRH-A group (standard deviation) N = 11**	**Mean difference (95% CI; P value)**
Carr 1995	Testosterone (nmol/L)	-1.20 (0.89)	-1.70 (1.08)	0.50 (95% CI -0.33 to 1.33; P value = 0.24)
Carr 1995	Free testosterone (pmol/L)	-7.3 (5.82)	-12.80 (6.85)	5.50 (95% CI 0.19 to 10.81; P value = 0.04)
Carr 1995	Androstenedione (nmol/L)	-2.00 (1.40)	-2.30 (1.41)	0.30 (95% CI -0.87 to 1.47; P value = 0.62)
Carr 1995	DHEAS (μmol/L)	-2.60 (4.97)	-0.40 (1.60)	-2.20 (95% CI -5.29 to 0.89; P value = 0.16)

Analysis 95.1. Comparison 95 GnRH-A 3.75 mg im every 28 days versus OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 14**	**Mean change from baseline in OCP group (standard deviation) N = 31**	**Mean difference (95% CI; P value)**
Creatsas 1993	Testosterone (nmol/L)	-0.40 (0.50)	-0.60 (0.74)	0.20 (95% CI -0.17 to 0. 57; P value = 0.29)
Creatsas 1993	SHBG (nmol/L)	6.30 (8.31)	6.20 (9.36)	0.10 (95% CI -5.36 to 5. 56; P value = 0.97)
Creatsas 1993	Androstenedione (ng/ml)	-0.70 (2.07)	-0.90 (3.21)	0.20 (95% CI -1.37 to 1. 77; P value = 0.80)
Creatsas 1993	DHEAS (nmol/L)	-0.70 (0.47)	-0.40 (2.36)	-0.30 (95% CI -1.17 to 0. 57; P value = 0.50)

Analysis 96.1. Comparison 96 GnRH-A 3.75 mg im every 28 days versus OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg), Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 12**	**Mean change from baseline in OCP group (standard deviation) N = 10**	**Mean difference (95% CI; P value)**
Elkind-Hirsch 1995	Testosterone (ng/dl)	-53.50 (14.47)	-29.40 (8.59)	-24.10 (95% CI -33.87 to -14.33; P value < 0.001)
Elkind-Hirsch 1995	Free testosterone (ng/dl)	-2.10 (0.83)	-1.30 (0.87)	-0.80 (95% CI -1.52 to -0.08; P value = 0.03)
Elkind-Hirsch 1995	SHBG (nmol/L)	0 (23.70)	116 (87.50)	-116 (95% CI -171.85 to -60.13; P value < 0.001)
Elkind-Hirsch 1995	DHEAS (µg/dl)	Authors state "no significant difference"	Authors state "no significant difference"	Cannot be calculated

Analysis 97.1. Comparison 97 GnRH-A 3.75 mg im every 28 days versus finasteride 5 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen (units not provided)**	**Mean change from baseline in GnRH-A group (standard deviation) N = 30**	**Mean change from baseline in finasteride group (standard deviation) N = 30**	**Mean difference (95% CI; P value)**
Bayhan 2000	Total testosterone	-0.30 (0.23)	-0.60 (0.72)	0.30 (95% CI 0.03 to 0.57; P value = 0.03)
Bayhan 2000	Free testosterone	-0.70 (0.55)	-0.90 (0.90)	0.20 (95% CI -0.18 to 0.58; P value = 0.30)
Bayhan 2000	Androstenedione	-0.90 (1.63)	-0.40 (0.74)	-0.50 (95% CI -1.14 to 0.14; P value = 0.13)
Bayhan 2000	DHEAS	-59 (69.02)	30 (84.29)	-89.00 (95% CI -127.98 to -50.02; P value < 0.001)
Bayhan 2000	SHBG	1.30 (0.42)	0.41 (0.45)	0.89 (95% CI 0.67 to 1.11; P value < 0.001)

Analysis 98.1. Comparison 98 GnRH-A 3.6 mg im every 28 days versus metformin 850 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in GnRH-A group (standard deviation) N = 20**	**Mean change from baseline from baseline in metformin group (standard deviation) N = 22**	**Mean difference (95% CI; P value)**
Cicek 2003	Total testosterone (ng/dl)	-25.9 (140.49)	-4.80 (183.71)	-21.10 (95% CI -119.51 to 77.31; P value = 0.67)
Cicek 2003	Free testosterone (pg/ml)	-0.6 (6.38)	-0.9 (7.66)	0.30 (95% CI -3.95 to 4.55; P value = 0.89)
Cicek 2003	DHEAS (μg/dl)	-72.4 (320.43)	-54.5 (517.14)	-17.90 (95% CI -275.62 to 239.82; P value = 0.89)
Cicek 2003	SHBG (nmol/l)	23.2 (117.31)	18.7 (83.06)	4.50 (95% CI -57.53 to 66.53; P value = 0.89)

Analysis 99.1. Comparison 99 Dexamethasone 0.37 mg per day compared to spironolactone 100 mg per day, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in dexamethasone group (standard deviation) N = 12	Mean change from baseline in spironolactone group (standard deviation) N = 12	Mean difference (95% CI; P value)
Carmina 1998	Testosterone (ng/dl)	-60 (10.39)	-12 (4.56)	-48.00 (95% CI -54.42 to -41.58; P value < 0.001)
Carmina 1998	Free testosterone (pg/ml)	-3.10 (1.09)	-0.40 (1.28)	-2.70 (95% CI -3.65 to -1.75; P value < 0.001)
Carmina 1998	DHEAS (µg/ml)	-2.60 (0.84)	0.20 (1.09)	-2.80 (95% CI -3.58 to -2.02; P value < 0.001)

Analysis 100.1. Comparison 100 Spironolactone 25 mg b.i.d. versus metformin 500 mg b.i.d., Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	Androgen	Mean change from baseline in spironolactone group (standard deviation) N = 34	Mean change from baseline in metformin group (standard deviation) N = 35	Mean difference (95% CI; P value)
Ganie 2004	Testosterone (nmol/L)	-1.63 (0.76)	-1.55 (1.04)	-0.08 (95% CI -0.51 to 0.35; P value = 0.71)
Ganie 2004	DHEAS (µmol/L)	-0.70 (1.66)	-0.90 (1.99)	0.20 (95%CI -0.66 to 1.06; P value = 0.65)

Analysis 101.1. Comparison 101 Clomiphene 50 mg once a day for 5 days starting at day 3 of the cycle versus metformin 1000 mg b.i.d., Outcome 1 Change in androgen levels.

Change in androgen levels

Study	Androgen	Mean change from baseline in clomiphene group (standard deviation) N = 165	Mean change from baseline in metformin only group (standard deviation) N = 172	Mean difference (95% CI; P value)
Roth 2012	Testosterone (ng/dl)	-2.6 (31.7)	-7.4 (27.6)	4.80 (95% CI -1.56 to 11.16; P value = 0.14)

Change in androgen levels (*Continued*)

Roth 2012	SHBG (nmol/L)	13.4 (16.0)	2.7 (13.5)	10.70 (95% CI 7.53 to 13.87; P value < 0.001)

Analysis 102.1. Comparison 102 Acarbose 150 mg to 300 mg per day versus placebo, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in acarbose group (standard deviation) N = 15 Ciotta 2001; N = 13 Penna 2005**	**Mean change from baseline in placebo group (standard deviation) N = 15 Ciotta 2001; N = 14 Penna 2005**	**Mean difference (95% CI; P value)**
Ciotta 2001	Testosterone (nmol/L)	-1.46 (0.33)	-0.10 (0.24)	-1.36 (5% CI -1.57 to -1.15; P value < 0.001)
Ciotta 2001	Androstenedione (nmol/L)	-2.34 (1.00)	-1.60 (1.06)	-0.74 (95% CI-1.48 to -0.00; P value < 0.05)
Ciotta 2001	DHEAS (µmol/ L)	-0.32 (1.01)	0.36 (0.95)	-0.68 (95% CI -1.38 to 0.02; P value = 0.06)
Ciotta 2001	SHBG (nmol/L)	13.60 (5.92)	-0.40 (4.90)	14.00 (5% CI 10.11 to 17.89; P value < 0.001)
Penna 2005	Testosterone (ng/dl)	-7.30 (13.99)	3.21(20.72)	-10.51 (95% CI -23.76 to 2.74; P value = 0.12)
Penna 2005	Androstenedione (ng/dl)	-1.34 (38.38)	4.30 (65.53)	-5.64 (95% CI -45.81 to 34.53; P value = 0.78)
Penna 2005	SHBG (nmol/L)	2.84 (4.96)	0.36 (6.03)	2.48 (95% CI -1.67 to 6.63; P value = 0.24)
Penna 2005				

Analysis 103.1. Comparison 103 Spearmint tea b.i.d. versus camomile tea b.i.d., Outcome 1 Change in androgen levels.

Change in androgen levels

Study	**Androgen**	**Mean change from baseline in spearmint tea group (standard deviation) N = 21**	**Mean change from baseline in camomile tea group (standard deviation) N = 20**	**Mean difference (95% CI; P value)**

Change in androgen levels (*Continued*)

Grant 2010	Free testosterone (pm/ml)	-1.48 (1.60)	-0.49 (1.81)	-0.99 (95% CI -2.04 to 0. 06; P value = 0.06)
Grant 2010	Testosterone (ng/ml)	-0.19 (0.24)	-0.07 (0.30)	-0.12 (95% CI -0.29 to 0. 05; P value = 0.16)
Grant 2010	DHEAS (µg/ml)	-1.20 (54.00)	3.80 (53.21)	-5.00 (95% CI -37.82 to 27. 82; P value = 0.77)

Analysis 104.1. Comparison 104 Low-frequency electro-acupuncture versus exercise 3 times a week for 30 minutes, Outcome 1 Changes in androgen levels.

Changes in androgen levels

Study	**Androgen**	**Mean change from baseline in acupuncture group (standard deviation) N = 24**	**Mean change from baseline in exercise group (standard deviation) N = 22**	**Mean difference (95% CI; P value)**
Jedel 2011	Testosterone (ng/ml)	-0.10 (0.14)	-0.04 (0.14)	-0.06 (95% CI -0.14 to 0. 02; P value = 0.15)
Jedel 2011	Free testosterone (pg/ml)	-2.21 (2.99)	-1.24 (2.66)	-0.97 (95% CI -2.60 to 0. 66; P value = 0.24)
Jedel 2011	Dihydrotestosterone (pg/ ml)	-23.2 (41.2)	-9.30 (34.2)	-13.90 (95% CI -35.72 to 7. 92; P value = 0.21)
Jedel 2011	DHEAS (µg/ml)	-0.29 (0.56)	-0.24 (0.55)	-0.05 (95% CI -0.37 to 0. 27; P value = 0.76)
Jedel 2011	SHBG (nmol/L)	3.52 (11.8)	7.30 (22.0)	-3.78 (95% CI -14.11 to 6. 55; P value = 0.47)

Analysis 105.1. Comparison 105 Low-frequency electro-acupuncture (14 treatments) versus no treatment, Outcome 1 Change in androgen levels.

Change in androgen levels

Study	**Androgen**	**Mean change from baseline in acupuncture group (standard deviation) N = 24**	**Mean change from baseline in control (no intervention) group (standard deviation) N = 13**	**Mean difference (95% CI; P value)**
Jedel 2011	Testosterone (ng/ml)	-0.10 (0.14)	0.01 (0.09)	-0.11 (95% CI -0.18 to -0. 04; P value = 0.004)

Change in androgen levels (*Continued*)

Jedel 2011	Free testosterone (pg/ml)	-2.21 (2.99)	0.03 (1.71)	-2.24 (95% CI -3.75 to -0.73; P value = 0.004)
Jedel 2011	Dihydrotestosterone (pg/ml)	-23.2 (41.2)	4.48 (31.9)	-27.68 (95% CI -51.60 to -3.76; P value = 0.02)
Jedel 2011	DHEAS (µg/ml)	-0.29 (0.56)	0.66 (3.40)	-0.95 (95% CI -2.81 to 0.91; P value = 0.32)
Jedel 2011	SHBG (nmol/L)	3.52 (11.8)	3.33 (12.7)	0.19 (95% CI -8.17 to 8.55; P value = 0.96)

Analysis 106.1. Comparison 106 Atorvastatin 20 mg once a day versus simvastatin 20 mg once a day, Outcome 1 Change in androgen levels.

Change in androgen levels

Study	**Androgen**	**Mean change from baseline in atorvastatin group (standard deviation) N = 32**	**Mean change from baseline in simvastatin group (standard deviation) N = 32**	**Mean difference (95% CI; P value)**
Kaya 2010	Total testosterone (ng/ml)	-0.16 (1.24)	-0.27 (1.56)	0.11 (95% CI -0.58 to 0.80; P value = 0.75)
Kaya 2010	DHEAS (µg/dl)	-4.40 (291.84)	4.80 (260.57)	-9.20 (95% CI -144.75 to 126.35; P value = 0.89)

Analysis 107.1. Comparison 107 Atorvastatin 20 mg once a day versus placebo once a day, Outcome 1 Change in androgen levels.

Change in androgen levels

Study	**Androgen**	**Mean change from baseline in atorvastatin group (standard deviation) N = 19**	**Mean change from baseline in simvastatin group (standard deviation) N = 18**	**Mean difference (95% CI; P value)**
Sathyapalan 2012	DHEAS (µmol/L)	-1.10 (0.61)	-0.30 (0.77)	-0.80 (95% CI -1.25 to -0.35; P value = 0.0005)
Sathyapalan 2012	Androstenedione (nmol/L)	-1.00 (0.48)	0.70 (2.30)	-1.70 (95% CI -2.78 to -0.62; P value = 0.002)

Analysis 108.1. Comparison 108 Bromocriptine 2.5 mg three times a day versus placebo, Outcome 1 Change in androgen levels.

Change in androgen levels

Study	**Androgen**	**Mean change from baseline in bromocriptine group (standard deviation) N = 7**	**Mean change from baseline in placebo group (standard deviation) N = 9**	**Mean difference (95% CI; P value)**
Murdoch 1987	Testosterone (nmol/L)	-0.9 (1.32)	-0.3 (0.30)	-0.60 (95% CI -1.60 to 0.40; P value = 0.24)
Murdoch 1987	Androstenedione (nmol/L)	-10.2 (8.20)	-7.7 (12.00)	-2.50 (95% CI -12.42 to 7.42; P value = 0.62)
Murdoch 1987	SHBG (nmol/L)	4 (13.23)	2 (9.00)	2.00 (95% CI -9.43 to 13.43; P value = 0.73)

ADDITIONAL TABLES

Table 1. Glossary of unfamiliar terms

Term	Definition
Acanthosis nigricans	Skin disorder in which there is darker, thick, velvety skin in body folds and creases. It is often found in people with obesity-related diabetes
Alopecia	Visibly-reduced hair density (can be diffuse, patchy, or patterned)
Anagen hair	Active growing hair
Anagen phase	Active growth phase of hair follicles (2 to 7 years)
Anovulation	An anovulatory cycle is a menstrual cycle during which the ovaries do not release an oocyte. Therefore, ovulation does not take place
Androgen	The generic term for any natural or synthetic compound, usually a steroid hormone, which stimulates or controls the development and maintenance of male characteristics by binding to androgen receptors
BMI (body mass index)	Weight in kilograms/height in metres
Box-and-whisker plot	Statistics assumes that your data points (the numbers in your list) are clustered around some central value. The 'box' in the box-and-

Table 1. Glossary of unfamiliar terms (*Continued*)

	whisker plot contains, and thereby highlights, the middle half of these data points. Box plots may also have lines extending vertically from the boxes (whiskers) indicating variability outside the upper and lower quartiles, hence the terms box-and-whisker plot
Catagen phase	Involution phase of the hair follicle
Effluvium	Loss of hair from the scalp or body
Galactorrhoea	Spontaneous flow of milk from the breast, unassociated with childbirth or nursing
Glabrous skin	External skin that is naturally hairless. It is found on the palmar surfaces of hands and fingers, soles of feet, lips, labia minora (inner vaginal lips), and glans penis
Gonadotropin-releasing hormone analogues (GnRH-analogues)	An analogue that activates the GnRH receptor. Chronic use inhibits secretion of follicle stimulating hormone and luteinising hormone by the pituitary gland resulting in decreased production of androgens by the ovaries
Hepatotoxic	Chemical-driven liver damage
Hyperandrogenism	Condition characterised by excessive production or secretion of androgens, or both
Hyperprolactinaemia	The presence of abnormally high levels of prolactin in the blood. Hyperprolactinaemia may cause production and spontaneous flow of breast milk and disruptions in the normal menstrual period in women
Hypertrichosis	Excessive (terminal and vellus) hair in non-androgen-dependent body sites, which varies in people with different ethnic backgrounds without any pathological findings
Hirsutism	Excessive hairiness on women in those parts of the body where terminal hair does not normally occur or is minimal - for example, beard or chest hair
Insulin resistance	Condition where the natural hormone insulin becomes less effective at lowering blood sugars
Metrorrhagia	Irregular bleeding between menstrual periods; menometrorrhagia is prolonged or excessive bleeding from the uterus
Oligo-ovulation	Infrequent, irregular ovulation
Postpartum	Period after birth

Table 1. Glossary of unfamiliar terms (*Continued*)

5α-reductase	An enzyme that converts testosterone, the male sex hormone, into the more potent hormone, dihydrotestosterone
Seborrhoea	Greasy skin caused by excess sebum
SHBG	Sex hormone-binding globulin
Telogen hair	Club hair or resting hair, prior to expulsion of hair canal by new anagen hair
Terminal hair	Thicker, longer, coarse pigmented hair
Vellus hair	Short, fine, light-coloured, and barely noticeable hair that develops on most of a person's body from childhood
Virilisation	The abnormal development of male sexual characteristics in a woman

Table 2. Interventions of the included studies

Lifestyle measures	
Low carbohydrate diet	Ghosh 2008
Low caloric diet	Pasquali 1986; Pasquali 2000
Low glycaemic index diet	Ghosh 2008
Moderate-intensity exercise programme	Brown 2009B; Jedel 2011; Stener-Victorin 2009; Vigorito 2007
Lifestyle modification (advice on diet/exercise/behaviour)	Hoeger 2004; Hoeger 2008
Topical therapies	
Eflornithine HCl 13.9% cream	Jackson 2007; Wolf 2007
Finasteride 0.25% or 0.5% cream	Iraji 2005; Lucas 2001
Fennel 1% and 2% cream	Javidnia 2003
Long-pulsed alexandrite laser + eflornithine 13.9% cream	Hamzavi 2007; Smith 2006
Oral contraceptive pills	
Ethinyl estradiol 35 μg + ethynodiol diacetate 1 mg	Azziz 1995

Table 2. Interventions of the included studies (*Continued*)

Ethinyl estradiol 20 µg + desogestrel 0.15 mg	Banaszewska 2007; Farina 2006
Ethinyl estradiol 30 µg + desogestrel 0.15 mg	Bhattacharya 2012; Breitkopf 2003; Creatsas 2000; Erkkola 1990; Hoeger 2008; Kriplani 2010; Levrier 1988; Mastorakos 2002; Mastorakos 2006; Porcile 1991; Porcile 1991B; Sanam 2011; Sobbrio 1990
Ethinyl estradiol 50 µg + desogestrel 0.15 mg	Porcile 1991
Ethinyl estradiol 30 µg + levonorgestrel 0.15 mg	Breitkopf 2003; Sanam 2011
Ethinyl estradiol 35 μg + cyproterone acetate 2 mg	Barth 1991; Batukan 2007; Belisle 1986 Bhattacharya 2012; Creatsas 2000; Elter 2002; Erkkola 1990; Harborne 2003; Ibáñez 2012; Lemay 2006; Luque-Ramírez 2007; Mastorakos 2002; Mastorakos 2006; Meyer 2007; Moltz 1984; Morin-Papunen 2000; Morin-Papunen 2003; Porcile 1991; Sabuncu 2003; Saeed 1993; Sahin 1998; Taheripanah 2010; Tartagni 2000; van Vloten 2002; Vegetti 1996; Vermeulen 1988; Wang 2012
Ethinyl estradiol 50 μg + cyproterone acetate 2 mg	Creatsas 1993; Holdaway 1985; Lachnit-Fixson 1977; Levrier 1988; Spuy 1995; Vermeulen 1988
Ethinyl estradiol 30 μg + drospirenone 3 mg	Battaglia 2010; Batukan 2007; Bhattacharya 2012; Farina 2006; Kriplani 2010; Lello 2008; Oner 2011; van Vloten 2002; Wang 2012
Ethinyl estradiol 20 μg + drospirenone 3 mg	Oner 2011; Fruzzetti 2010
Triphasic OCP (30, 40, and 30 μg ethinyl estradiol and 50, 75, and 125 μg levonorgestrel)	Calaf 2007
Ethinyl estradiol 35 μg + norethindrone 1 mg	Carr 1995; Heiner 1995
Ethinyl estradiol 35 μg + norgestimate 0.25 mg	Allen 2005; Cibula 2005
Ethinyl estradiol 30 μg + chlormadinone acetate 2 mg	Kaiser 1984; Lello 2008
Ethinyl estradiol 35 μg + norethindrone 0.4 mg	Elkind-Hirsch 1995
Norethisterone 1 mg and mestranol 50 µg	Kaiser 1984
Ethinyl estradiol 50 μg + D-norgestrel 0.25 mg	Lachnit-Fixson 1977
Ethinyl estradiol 30 μg + gestodene 75 µg	Sobbrio 1990
Antiandrogens	

Table 2. Interventions of the included studies (*Continued*)

Cyproterone acetate	Barth 1991; Lumachi 2003; Schmidt 1987
Flutamide	Erenus 1994; Esmaeilzadeh 2010; Falsetti 1999; Fruzzetti 1999; Gambineri 2006; Ibáñez 2002; Moghetti 2000; Müderris 2000; Paoletti 1999; Venturoli 1999
Ketoconazole	Akalin 1991; Cedeno 1990; Venturoli 1999
Spironolactone	Carmina 1998; Erenus 1994; Erenus 1997; Ganie 2004; Lumachi 2003; McLellan 1989; Moghetti 2000; Prezelj 1989; Spritzer 2000
5α reductase inhibitors	
Finasteride	Al-Khawajah 1998; Bayhan 2000; Bayram 2002: Beigi 2004; Ciotta 1995; Erenus 1997; Falsetti 1999; Fruzzetti 1999; Lakryc 2003; Lumachi 2003; Moghetti 2000; Müderris 2000; Sahin 1998; Tartagni 2004; Venturoli 1999
Insulin sensitising agents	
Metformin	Ahmad 2008; Allen 2005; Ashrafinia 2009; Banaszewska 2011; Cicek 2003; Crave 1995; Eisenhardt 2006; Esmaeilzadeh 2010; Gambineri 2006; Ganie 2004; Harborne 2003; Hoeger 2004; Hoeger 2008; Ibáñez 2002; Ibáñez 2011B; Kelly 2002; Kjøtrød 2004; Ladson 2011; Luque-Ramírez 2007; Maciel 2004; Meyer 2007; Moghetti 2000B; Morin-Papunen 2000; Morin-Papunen 2003; Navali 2012; Onalan 2005; Oner 2011B; Ortega-González 2005; Otta 2010; Roth 2012
Pioglitazone	Aigner 2009; Brettenthaler 2004; Navali 2012; Ortega-González 2005
Rosiglitazone	Ahmad 2008; Dereli 2005; Lam 2011; Lemay 2006; Rautio 2005
Troglitazone	Azziz 2001
Gonadotropin-releasing analogues	
GnRH analogue (leuprolide)	Azziz 1995; Bayhan 2000; Carr 1995; Elkind-Hirsch 1995; Falsetti 1992; Falsetti 1994; Falsetti 1994B; Rittmaster 1990
GnRH analogue (goserelin)	Cicek 2003; Tiitinen 1994
GnRH analogue (triptorelin)	Carmina 1994; De Leo 2000
GnRH analogue (nafarelin nasal spray)	Heiner 1995
Other therapies	

Table 2. Interventions of the included studies (*Continued*)

Acarbose	Ciotta 2001; Penna 2005
Clomiphene citrate 50 to 100 mg/day on day 3 to 7	Elnashar 2006; Roth 2012
Combined contraceptive vaginal ring (15 μg ethinyl estradiol + 120 μg etonogestrel)	Battaglia 2010
Ovarian diathermy	Ashrafinia 2009; Farquhar 2002
Ultrasound-guided transvaginal needle ovarian drilling	Badawy 2009b
Laparoscopic electrosurgery ovarian drilling	Badawy 2009b
Atorvastatin	Kaya 2010; Sathyapalan 2012
Simvastatin	Banaszewska 2007; Banaszewska 2011; Kaya 2010
Dexamethasone	Carmina 1998
Prednisone 100 to 200 µg/kg	Rittmaster 1988
Myo-inositol	Ciotta 2012
D-chiro-inositol	Ciotta 2012; Ciotta 2012B
D-Tr-6-LHRH	Creatsas 1993
Camomile tea	Grant 2010
Spearmint tea	Grant 2010
Electro acupuncture	Jedel 2011; Stener-Victorin 2009
Bromocriptine	Murdoch 1987
Cimetidine	Lissak 1989
N-acetyl-cysteine	Oner 2011B
Octreotide-LAR	Gambineri 2005
Sibutramine	Sabuncu 2003
Combination therapies	
Hypocaloric diet + cyproterone acetate 50 mg/day (10 days) + ethinyl estradiol 50 μg (21 days)	Pasquali 1986

Table 2. Interventions of the included studies (*Continued*)

Hypocaloric diet (1200 to 1400 kcal/day) + metformin	Pasquali 2000
Diet 1200 kcal + 6-D tryptophane luteinizing hormone-releasing hormone	Couzinet 1986
Life style modification + metformin	Hoeger 2004
Clomiphene citrate + dexamethasone 2 mg/day on day 3 to 12	Elnashar 2006
Dexamethasone + spironolactone	Carmina 1998; Prezelj 1989
Simvastatin + metformin	Banaszewska 2011
Pioglitazone + flutamide + metformin	Ibáñez 2012
Flutamide + metformin	Gambineri 2006; Ibáñez 2002; Ibáñez 2003
Pioglitazone + transdermal contraceptive (ethinyl estradiol 600 µg + norelgestromin 6 mg) + metformin + flutamide	Ibáñez 2009
Transdermal contraceptive (ethinyl estradiol 600 µg + norelgestromin 6 mg) + metformin + flutamide	Ibáñez 2009
OCP (ethinyl estradiol 35 μg + norgestimate 250 μg) + metformin	Cibula 2005
OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + cyproterone acetate (variable dose)	Barth 1991; Belisle 1986; Erenus 1996; Kelekci 2012; Moltz 1984
OCP (ethinyl estradiol 0.01 mg/day for 10 days, 0.02 mg/day for the next 11 days and 7 'pause' days) + cyproterone acetate	Venturoli 1998
OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg) + cyproterone acetate (variable dose)	Holdaway 1985; Huber 1985
OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + sibutramine	Sabuncu 2003
OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + spironolactone	Kriplani 2009
OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) + finasteride	Kriplani 2009; Tartagni 2000
OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) + metformin	Elter 2002

Table 2. Interventions of the included studies (*Continued*)

OCP (ethinyl estradiol 30 μg + desogestrel 0.15 mg) + spironolactone	Erenus 1996
OCP (ethinyl estradiol 20 μg + drospirenone 3 mg) + metformin	Fruzzetti 2010
OCP (ethinyl estradiol 20/30 μg + drospirenone 3 mg) + cyproterone acetate	Fruzzetti 2010; Kelekci 2012
OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) + spironolactone	Kelekci 2012
OCP (ethinyl estradiol 20 μg + levonorgestrel 0.1 mg) + spironolactone	Meyer 2007
OCP (ethinyl estradiol 35 μg + norethisterone 0.5 mg) + spironolactone	Dixon 1991
Triphasic OCP + spironolactone 100 mg/day	Cusan 1994; O'Brien 1991
Triphasic OCP + flutamide	Calaf 2007; Cusan 1994; Pazos 1999
Triphasic OCP + cyproterone acetate	Pazos 1999; Venturoli 1998; Venturoli 1999
Cyproterone acetate 50 mg + estradiol valerate 2 mg	Consoli 1994; Vexiau 1995
Cyproterone acetate 25 mg + ethinyl estradiol 20 μg	Beigi 2004; Fruzzetti 1999
Cyproterone acetate 50 mg + transdermal estradiol 50 mg	Consoli 1994; Vexiau 1995
Cyproterone acetate 50 to 100 mg + ethinyl estradiol 30 to 35 μg	Dixon 1991; O'Brien 1991; Spritzer 2000
Cyproterone acetate 50 mg + 1200 kcal diet	Couzinet 1986
GnRH-A (triptorelin) + oestrogens	Carmina 1994
GnRH-A (leuprolide) + OCP (ethinyl estradiol 35 μg + norethindrone 1 mg)	Carr 1995
GnRH-A (goserelin) implant + oestrogen-progestin replacement	Tiitinen 1994
GnRH-A (goserelin) + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg)	Vegetti 1996
GnRH analogue (triptorelin) + OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg)	De Leo 2000
GnRH analogue (goserelin) + OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg)	Spuy 1995

Table 2. Interventions of the included studies (*Continued*)

GnRH analogue (triptorelin) + flutamide 250 mg	De Leo 2000
GnRH analogue (leuprolide) + OCP (ethinyl estradiol 35 µg + norethindrone 0.4 mg)	Elkind-Hirsch 1995
GnRH analogue (leuprolide) + OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg)	Falsetti 1992; Falsetti 1994; Falsetti 1994B
GnRH analogue (leuprolide) + dexamethasone	Rittmaster 1990
GnRH analogue (triptorelin) + triphasic OCP	Pazos 1999
Nafarelin nasal spray 400 µg b.i.d. + OCP (norethindrone 1 mg + ethinyl estradiol)	Heiner 1995
Clomiphene citrate + metformin	Roth 2012; Zheng 2005
Clomiphene citrate 100 mg/day on day 3 to 7 + dexamethasone 2 mg/day on day 3 to 12	Elnashar 2006
Clomiphene citrate + rosiglitazone	Zheng 2005
3 cycles of urinary gonadotropins or recombinant follicle-stimulating hormone	Farquhar 2002

b.i.d.: twice a day
GnRH: gonadotropin-releasing hormone
OCP: oral contraceptive pill

Table 3. Included studies with no usable or irretrievable data

Study ID	Interventions and comparisons	N	Comments
Akalin 1991	Ketoconazole 600 mg versus placebo	11	No separate data for each of the 2 treatment periods (cross-over design), no wash-out period
Brown 2009B	Moderate-intensity exercise programme versus no change in lifestyle	37	None of our outcomes were assessed
Cibula 2005	OCP (ethinyl estradiol 35 µg/norgestimate 250µg) versus OCP (ethinyl estradiol 35 µg/norgestimate 250µg) + metformin 1500 mg/day	30	Unclear how many women with PCOS were hirsute

Table 3. Included studies with no usable or irretrievable data (*Continued*)

Consoli 1994	Cyproterone acetate 50 mg + estradiol valerate 2 mg per os versus cyproterone acetate 50 mg + transdermal estradiol 50 mg	67	No separate data for women with hirsutism
Couzinet 1986	Cyproterone acetate versus 6-D tryptophane LHRH	10	Cross-over design, no separate data at end of first period, nor baseline data for second period
Crave 1995	Metformin versus placebo	24	Unclear how many women in each treatment arm
Creatsas 2000	OCP (desogestrel 0.15 mg + ethinyl estradiol 30 μg) versus OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg)	24	No end data for F-G score, PI did not reply, no usable data
Elnashar 2006	Clomiphene citrate + dexamethasone versus clomiphene citrate + placebo	80	No separate data for women with hirsutism
Erenus 1997	Finasteride versus spironolactone	40	60% drop-outs
Erkkola 1990	Cyproterone acetate 2 mg + ethinyl estradiol 35 μg versus desogestrel 0.150 mg + ethinyl estradiol 0.03 mg	162	No separate data for women with hirsutism
Farina 2006	OCP (ethinyl estradiol 30 μg + drospirenone 3 mg) versus OCP (ethinyl estradiol 40 to 30 μg + desogestrel 25 to 125 μg)	120	Inconsistent and incomplete reporting of outcomes data across intervention groups. No reliable or usable data
Farquhar 2002	Laparoscopic ovarian diathermy versus gonadotropins	50	No separate data for women with hirsutism, only one secondary outcome of our review was addressed (ovulation)
Gambineri 2005	Octreotide LAR versus placebo	20	No separate data for women with hirsutism
Ghosh 2008	Low carbohydrate diet for 6 months versus low glycaemic index diet for 6 months	24	Abstract, limited data, unclear how many women were hirsute
Holdaway 1985	Maintenance therapy with OCP (including 2 mg cyproterone acetate) + 25 mg cyproterone acetate versus OCP (including 2 mg cyproterone acetate) + placebo	35	No wash-out period after first 9 months, thereafter cross-over design, with no wash-out period. No separate data for baseline and end of treatment period for each of the 3 time periods were reported

Table 3. Included studies with no usable or irretrievable data (*Continued*)

Huber 1985	Cyproterone acetate 300 mg im + OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg) versus cyproterone acetate 100 mg orally for 10 days + OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg)	10	Abstract. Limited data reported. Unclear if there were 2 groups of 5
Ibáñez 2003	Flutamide + metformin versus flutamide + metformin, only starting at different time points	30	Intervention and comparator were identical, participants "randomised to" timing of start of treatment
Ibáñez 2011B	Metformin versus metformin	38	Intervention and comparator were identical, participants "randomised to" timing of start of treatment
Kaiser 1984	OCP (combination of ethyl estradiol and chlormadinone acetate) versus OCP (1 mg norethisterone and 50 µg mestranol)	80	Paper describes 2 studies. In the first study, all participants receive the intervention, in the 2nd study participants are randomised. No wash-out period between the 2 studies. Unclear how many women were hirsute
Kelly 2002	Metformin versus placebo	16	No end of first phase data no baseline data for second phase
Kjøtrød 2004	Metformin versus placebo	73	Only 37% of women were hirsute and no separate data for those. Furthermore, none of our outcomes were assessed
Lachnit-Fixon 1977	OCP (ethinyl estradiol 50 μg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 50 μg + 0. 25 mg D-norgestrel)	88	Unclear how many women were hirsute and no exact data on the effect on hirsutism (only no difference between the treatment groups)
Ladson 2011	Metformin versus placebo	114	Drop-out rate > 40% (67%)
Levrier 1988	OCP (ethinyl estradiol 30 μg + 150 μg desogestrel) versus (ethinyl estradiol 50 μg + 2 mg cyproterone acetate)	69	Only few of the women had hirsutism, unclear how many in each group as only several locations are provided and not number of participants
Lemay 2006	Rosiglitazone versus OCP (ethinyl estradiol 35 μg + 2 mg CPA)	28	Drop-outs in OCP arm > 40% (46.2%)
Mc Lellan 1989	Spironolactone versus placebo	38	Drop-outs > 40%
Meyer 2007	Metformin versus OCP (ethinyl estradiol 35 μg + 2 mg CPA) versus OCP (ethinyl estradiol 30 µg + levonorgestrel 100 µg) + spironolactone 50 mg	110	Unclear how many women with PCOS were hirsute, the mean hirsutism score was only > 8 in the metformin group

Table 3. Included studies with no usable or irretrievable data (*Continued*)

Moltz 1984	OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg) + 10 mg cyproterone acetate versus OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg)	164	Unclear how many dropped out in control group, unclear how many were hirsute in control group. Mainly data are reported on the OCP + CPA group, and hardly any data on control group
Morin-Papunen 2000	OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus metformin	32	Drop-outs 44%
Morin-Papunen 2003	OCP (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) versus metformin	17	No separate data on women that were hirsute, means of Ferriman-Gallwey score in both groups were below threshold for hirsutism (Ferriman-Gallwey score > 8)
Oner 2011B	Metformin versus N-acetyl-cysteine	100	Imbalance in losses to follow-up with 40% losses in metformin arm and 10% in the N-acetyl-cysteine arm
Ortega-González 2005	Pioglitazone versus metformin	57	Drop-outs in one arm 43%
Paoletti 1999	Flutamide versus placebo	22	No separate Ferriman-Gallwey scores per arm, only per group of women with idiopathic hirsutism and per women with PCOS, and the only other outcome that matched our inclusion criteria was adverse events, which was not reported
Pasquali 1986	Hypocaloric diet + cyproterone acetate/ethinyl estradiol versus hypocaloric diet	14	Unclear how many women with PCOS were hirsute
Pasquali 2000	Hypocaloric diet + metformin versus hypocaloric diet + placebo	40	13/40 were hirsute, no separate data on hirsute women
Rittmaster 1988	Prednisone every day versus prednisone every other day	8	No wash-out period between treatment schedules, no separate end data/baseline data at 4 months, no data on hirsutism score
Rittmaster 1990	Leuprolide + dexamethasone versus leuprolide + placebo	20	No wash-out phase. No baseline data for second phase per treatment arm. Data are provided for idiopathic hirsutism and PCOS, but not clear per treatment arm. Protocol deviation biasing therapeutic comparisons in addition to inconsistency and incompleteness in outcome reporting did not permit a clear analysis and interpretation of results
Sanam 2011	OCP (ethinyl estradiol 30 µg + desogestrel 150 µg) versus OCP (ethinyl estradiol 30 µg + levonorgestrel 150 µg)	100	The mean of the F-G score as reported (between 2 and 3) does not match the recognised criteria for hirsutism (should be > 8; Hatch 1981). No separate data for hirsute women
Schmidt 1987	Cyproterone acetate im versus cyproterone acetate orally	20	Inconsistent data reporting, lack of clarity about missing outcome data and about withdrawals and losses

Table 3. Included studies with no usable or irretrievable data (*Continued*)

Spuy 1995	OCP (cyproterone acetate/ethinyl estradiol) versus OCP (cyproterone acetate/ethinyl estradiol) + GnRH agonist analogue	34	Abstract from conference proceedings, limited data reported
Stener-Victorin 2009	Low-frequency electro acupuncture versus physical exercise versus untreated control	84	Only data reported on 20/84 participants (24%)
Unfer 2000	Ethinyl estradiol 20 µg/day for 3 weeks + the first 10 days cyproterone acetate 12.5 mg/day versus flutamide	40	Abstract from conference proceedings, limited data reported
van Vloten 2002	OCP (ethinyl estradiol 30 µg + 3 mg drospirenone) versus OCP (OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg)	128	Few hirsute women included, no separate data for hirsute women
Venturoli 1999	Flutamide versus finasteride versus ketoconazole versus OCP (ethinyl estradiol 0.01 mg/day for the 1st week, 0.02 mg/day for the 2nd week, 0.01 mg/day for the 3rd week and 7 'pause' days) + cyproterone acetate 12.5 mg/day for the first 10 days	66	Women with nonclassic adrenal hyperplasia included, no separate data for women with PCOS and idiopathic hirsutism
Vermeulen 1988	OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 50 µg + cyproterone acetate 2 mg)	30	Unclear how many were hirsute, no separate data for hirsute women
Vexiau 1995	Cyproterone acetate with 17β estradiol by transdermal patch versus cyproterone acetate with 17β estradiol valerate orally	65	Unclear how many were hirsute, no separate data for hirsute women, and none of our outcomes are assessed
Visnovský 2010	OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 30 µg + dienogest 2 mg) versus OCP (ethinyl estradiol 30 µg + drospirenone 3 mg)	90	54/90 were hirsute, no separate data for hirsute women
Wang 2012	OCP (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) versus OCP (ethinyl estradiol 30 µg +	110	abstract from conference proceedings, limited data reported

Table 3. Included studies with no usable or irretrievable data (*Continued*)

	drospirenone 3 mg)		

CPA: cyproterone acetate
F-G score: Ferriman-Gallwey score
GnRH: gonadotropin-releasing hormone
im: intramuscular
OCP: oral contraceptive pill
PCOS: polycystic ovary syndrome
per os: orally
PI: principal investigator

Table 4. Contact with investigators

Study ID	Response	Additional	Comment
Ahmad 2008	Email: jamalahmad11@rediffmail.com (sequence generation and concealment) 10-3-13, 27-3-2013, 30-4-2013,14-5-2013 Reply 17-5-2013/ 27-5-2013. No trial details provided but promised to reply Resent 02-06-2013, 09-06-2013, 29-6-2013	No	
Aigner 2009/Brettenhaler 2004	10-3-2013 c.datz@kh-obdf.salzburg.at (sequence generation and allocation concealment) and 5/40 were lost to follow up. How many from each group and were there any reasons for this? New mail of me 11-3-2013 cdegeyter@uhbs.ch; ukeller@uhbs.ch Reply 21-3-2013: ulrich.keller@unibas.ch Dear Dr. Zuuren thank you for your mail. I am somewhat surprised that I heard the first time that another paper had been pulled out of our pioglitazone study (I was the senior author and PI of the	Yes	

Table 4. Contact with investigators (*Continued*)

	earlier study after all) - …remarkable behaviour of CDG and NB (formerly Brettenthaler now Bachofner)… I will try to find the details of the protocol of the JCEM paper 2004 and let you know. Kind regards later mail; Dear Dr. van Zuuren according to the records the randomization was performed by the hospital pharmacy using a random number generator (such as used in EXCEL). The pharmacy prepared tablets with 30 mg pioglotazone or matching placebo tablets. Neither patients nor physicians knew about the allocation until the end of the trial. I hope this helps, kind regards. "Sorry I am not sure if I understand your question. Blinding and allocation concealment to me are the same with other words. Blind is blind, is it not? The pharmacy delivered "neutral" boxes or containers identical for verum and placebo with numbers, the numbers were generated in random order by the pharmacy and neither doctors nor patients knew the content nor the key." 17-4-2013 mail Dear professor Keller, We have found one inconsistency with the paper of Brettenhaler 2004 and that is the Ferriman-Gallwey score after 3 months for the placebo group which was 15.8 (2.8) in the 2009 paper (Aigner et al), but 15.9 (1.9) in the 2004 paper (Brettenthaler et al). Can you please confirm what the correct end value is of the FG score for the placebo group after 3		

Table 4. Contact with investigators (*Continued*)

	months? 18-4-2013 Dear Dr van Zuuren I checked the data from the Brettenthaler Paper 2004, I found in the EXCEL tables from 2002 that the 3 month Placebo value of the FG Score was correct (15.9 +/- 1.9) I have not been involved in the Aigner Paper and I can not tell you why they came up with slightly different numbers All other numbers e.g. age and BMI are identical in the 2 papers - so I suspect it was a typing error? If you want to be sure you have to ask Aigner or Nora Bachofner (whose name was Brettenthaler when she was in Basel, before she was married) Kind regards Ulrich Keller, Prof. Dr.med.		
Allen 2005	10-3-2013 holley. allen@bhs.org (allocation concealment) and are there 36 or 35 patients randomized? In abstract it states 35, and under patients and methods 36? Reply 11-3-2013 Dear Prof. Zuuren, Using a computerized random number generator an allocation sequence was determined. Allocation assignment for each subject number was marked on a paper, individually sealed in a concealing bank envelope by staff not involved in patient care or the clinical portion of the study prior to randomization of the first patient. The correct number is 35, with 4 drop outs and 31 subject analyzable. Thanks. I look forward to your	Yes	

Table 4. Contact with investigators (*Continued*)

	results. Please let me know if I can be of further help. Regards, Holley Allen		
Ashrafinia 2009	Email hosp_arash@tums.ac.ir (sequence generation) 23-7-2013 Resent 8-8-2013, 25-08-2013. No response	No	
Badawy 2009B	10-3-2013 ambadawy@yahoo.com (allocation concealment) and the baseline values for testosterone in each group Resent 27-3-2013 Resent 30-4-2013 Resent 14-5-2013 Reply 18-05-2013 Dear, The method of concealment was sealed envelops after computeri- generated random table allocation. Basal testosterone is not available to me now. Best regards Ahmed Badawy, MSC MD FRCOG PhD Professor of OB/GYN Mansoura University, Egypt	Yes	
Banaszweska 2007	10-3-2013 antoni.duleba@yale.edu: Baseline data for each group for the first treatment period The data at 12 weeks (end of first treatment period) for each of the 2 groups Reply 11-3-2013 2 attachments: Dear Dr. Van Zuuren, Please note that the table presents means and not geometric means as we did in the original paper. I also enclose automatic printout from our statistical analysis program. Kind regards, ajd	Yes	

Table 4. Contact with investigators (*Continued*)

Bayhan 2000	Email: bayhan@tr-net.net.tr (e-mail of 1999) ; mbahceci@dicle.edu.tr; gbayhan@dicle.edu.tr (e-mail invented by me); mertem@dicle.edu.tr; ahmetyalinkaya@ixir.com (sequence generation, concealment, losses to follow-up) 6-4-2013	Not applicable	None of the e-mail addresses were correct
Bayram 2002	Email: fbayram@erciyes.edu.tr (sequence generation, concealment, losses to follow-up, ITT or PP) 6-4-2013 Resent 30-4-2013,15-5-2013, 2-6-2013. No response	Not applicable	
Beigi 2004	Email: beigi_a@yahoo.com (sequence generation, concealment) 8-4-2013 Resent 30-4-2013,14-5-2013, 02-6-2013. No response	Not applicable	
Calaf 2007	Email: jcalaf@hsp.santpau.es (sequence generation, concealment, losses to follow-up) 19-4-2013 Resent 30-4-2013, 14-5-2013 Reply 15-5-2014 Incomplete reply no additional detail Resent 02-06-2013, 09-06-2013, 29-06-2013	No	
Ciotta 1995	Email lilliana.ciotta@tin.it 21-4-2013 Resent 12-05-2013, 2-6-2013	Not applicable	
Ciotta 2001	Email lilliana.ciotta@tin.it (concealment, blinding, losses to follow-up) 22-4-2013 Resent 12-05-2013, 02-06-2013. No response	Not applicable	
Ciotta 2012B	Email lilliana.ciotta@tin.it (concealment, blinding, losses to follow-up)	Not applicable	

Table 4. Contact with investigators (*Continued*)

	Resent 12-05-2013, 02-06-2013. No response		
Colonna 2012	Email l.colonna@idi.it (Sequence generation, concealment) 24-4-2013 Resent 19-5-2013, 02-06-2013. No response	Not applicable Appeared to include same data as 2008 (Copub)	
Cosma 2008	12-05-2014 Dear professor Montori, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and we read your Systematic review "Insulin Sensitizers for the Treatment of Hirsutism: A Systematic Review and Metaanalyses of Randomized Controlled Trials" J Clin Endocrinol Metab, April 2008, 93(4):1135-1142 Can you maybe help us how the quality of evidence was rated? The article refers to "The Endocrine Society Task Force on Hirsutism, assembled to produce clinical practice guidelines, commissioned these metaanalyses to support the formulation of evidence-based recommendations" but what method was used? Response 12-05-2014 I am a little confused by your question given that the quality assessment and its results are described in the paper with headings that indicate so. For example, we describe the method under the section "Quality Assessment": Quality assessmentTo ascertain the reported methodological quality of eligible trials,pairs of reviewers (M.C., B.A.S., D.		

Table 4. Contact with investigators (*Continued*)

	M.K., M.L.L., R.J.M., and V. M.M.),working independently and with adequate reliability, determined the adequacy of allocation concealment (0.56) and blinding of patients(0.69), healthcare providers (0.63), and outcome assessors (0.88). The proportion of participants randomized for whom the trial authors did not report hirsutism outcomes (i.e. the extent of loss to follow-up) was also noted. The paper also reports the results of this assessment. The full text of the paper can be found here: http://press.endocrine.org/doi/pdf/10.1210/jc.2007-2429 Our reply: Dear professor Montori, I did not refer to limitations in study designs as done in risk of bias assessment in Cochrane reviews, but I referred to how decisions were made on low or very low **quality of evidence**? So I did not refer to methodological quality, but quality of the evidence. How did you decide on that? There are several systems/methods how to rate quality of evidence. Best regards Esther Reply: No, we just noticed those issues and reported on them. No scale, risk of bias or other summative approach were used.V Our reply: Thank you, based on the wording we thought GRADE was used to rate the level of evidence (which includes limitations in study design, indirectness, imprecision, inconsistency, publication bias etc) and as we saw you also worked on the GRADE guidelines.		

Table 4. Contact with investigators (*Continued*)

	Reply: Grade was used to determine high, moderate, low, and very low quality for the guidelines I do not recall if we were using GRADE explicitly for quality assessment in the reviews at that time. V 2-6-2014: Murad.Mohammad@mayo.edu sent different GRADE tables on Cosma, Swiglo 2008		
Creatsas 1993 and 2000	Email: geocre@aretaieio.uoa.gr (sequence generation, concealment, blinding, baseline values, losses to follow-up) 26-4-2014 Resent 12-5-2013, 2-6-2013. No response	Not applicable	
De Leo 2000	deleo@unisi.it e-mail sent 30-4-2013 Dear professor de Leo My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Hormonal and clinical effects of GnRH agonist alone, or in combination with a combined oral contraceptive or flutamide in women with severe hirsutism. Gynecological Endocrinology 2000;14(6):411-6.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. Were the obese patients randomised separately?, as it is a bit unclear that on page 412 it states that patients were ran-	Yes	

Table 4. Contact with investigators (*Continued*)

	domly divided in 3 groups of 12, and on page 413 it states that the obese patients were randomly assigned, 4 to each group? 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). Who had access to the random number table? Thank you so much for your efforts. Resent 12-5-2013 Resent 2-06-2013 Reply 3-6-2013 Dear dr, Zuure, I apologize for delay,but I was in holiday. Regarding your questions, I remember that the obese women were 4 in each group and the randomised was done separately to be secure to have same number of obese patients in all groups. All women were randomised before different protocols. e-mail of evz: Thank you professor De Leo, And how was the allocation concealed (my 2nd question) ? Could the upcoming assignment been foreseen by the investigator or patient?, and if not, what method was used to make sure they did not know in which treatment arm they would end up? Was the random number table accessible to investigators or participants?		

Table 4. Contact with investigators (*Continued*)

	4-6-2013: Dear dr.Ester van Zuure, the study is very old and my priciple collaborator now works in other place. I remember that all women didn't know what kind of treatments they should be inserted , the patients asked only to improve their hyperandrogenic simptoms		
Dereli 2005	Unable to find a recent e-mail address, or recent working address	Not applicable	
Eisenhardt 2006	stefan.eisenhardt@med. uni-heidelberg.de mail is incorrect 3-5-2013 eisenhardt-praxis@t-online.de Dear professor Eisenhardt My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Early Effects of Metformin in Women with Polycystic Ovary Syndrome: a prospective randomized, double-blind, placebo controlled trial ***J Clin Endocrinol Metab*** 91:946-952, 2006) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. What were the specific measures used to blind personnel and patients from knowledge of which intervention a participant received (how was the double blinding done)? 2.Instead of the provided medians (1-3 quartiles), could you help us with Means SD's	Yes	

Table 4. Contact with investigators (*Continued*)

	or SEM's (baseline and at end of study), for the Ferriman-Galwey scores, testosterone, DHEAS, androstenedione, SHBG and BMI? Resent 12-5-2013 14-5 reply Dear Dr. van Zuuren, thanks for being interested in our study from former days. I sent your Email-Request to Prof. Strowitzki - hopefully he can answer and help you with your questions 27-5- 2013 thomas_strowitzki@med.uni-heidelberg.de sent again Resent 02-6-2013 Reply 3-6-2013 Dear Dr van Zuuren I apologize for the delay. The reason is that we have some difficulties with the raw data. Data collection was done approximately 2005. The statistician has left our medical faculty. So we have no further access to the statistical data. Furthermore we are currently moving to a completely new building and a lot of data got lost. The first author Stefan Eisenhardt is also no longer working in the department. I have checked all my archives, but I don't possess the original data. I apologize for this inconvenience. Kind regards T. Strowitzki		
Elnashar 2006	Email: elnashar53@hotmail.com e-mail (sequence generation, SD or SE, separate data for hirsute women) 3-5-2013 Resent 12-5-2013, 02-6-2013. No response	Not applicable	

Table 4. Contact with investigators (*Continued*)

Elter 2002	Email: korayelter@marmara.edu.tr (sequence generation, concealment) 3-5-2013 Resent 12-5-2013, 2-6-2013	Not applicable	
Fruzetti 2010	ffruzzi@tin.it sent 6-5-2013 Dear Professor Fruzzetti, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Comparison of effects of 3 mg drospirenone plus 20 ug ethinyl estradiol alone or combined with metformin or cyproterone acetate on classic metabolic cardiovascular risk factors in nonobese women with polycystic ovary syndrome. Fertility and Sterility 2010;94(5):1793-8) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial detail: 1. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) Resent 2-6-2013 Reply 03-06-2013 sorry for my delay but I am out of my Office. I can answer within a few days thank you	No	

Table 4. Contact with investigators (*Continued*)

	franca fruzzetti 12-06-2013 Dear Esther sorry for the delay but as I wrote you I was out of my office . As for your answer please note that at the time of the enrollement the intervention allocations, i.e. the type of combination to be administered, have not been known in advance by the physician 12-06-2013 Thanks for your reply. I sent out more than 20 e-mails to people, so sorry if I chased you. I understand that it was not known, but how was this protected? How did you make sure that the allocation could not been foreseen by patients or investigators. What method was used that until they had the treatment in their hands nobody knew. It states that one of the investigators decided on the allocation sequence...so that investigator (Daria Perini) knew? Thanks for your time		
Gambineri 2004	Email: renato.pasquali@unibo.it (sequence generation, concealment, blinding, baseline data) 7-5-2013 Resent 13-5-2013, 2-6-2013, 29-6-2013. No response	Not applicable	
Gambineri 2005	Email: renato.pasquali@unibo.it (sequence generation, concealment, blinding) 7-5-2013 Resent 2-6-2013, 29-6-2013. No response	Not applicable	
Gambineri 2006	'alessandra.gambiner3@unibo.it' and renato.pasquali@unibo.it Dear professor Gambineri and professor Pasquali,	Not applicable	

Table 4. Contact with investigators (*Continued*)

	I have sent already 2 mails to professor Pasquali on the papers of 2004 and 2005 you had together in women with PCOS, but we now have some additional questions on the 2006 study (Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. Journal of Clinical Endocrinology and Metabolism 2006;91(10):3970-80.) As said in my earlier mails, my colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and several of your studies have been identified as potentially eligible for inclusion. We now like to discuss the 2006 publication mentioned above To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. 40 of the eighty patients had already started in 2004 for six months. Were all 80 randomised prior to start of 2004 study or only 40 ? Fig 1 in 2006 study shows all 80 randomised at one time? 2. How were data pooled for 40 from 2004 at the 12 month period when the 40 from 2006 were only 6 months into that study? 3. the method used to con-		

Table 4. Contact with investigators (*Continued*)

	ceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). Quote "The allocation sequence of the treatments was decided by a third party (A.V.) before the recruitment of the patients by random number tables." So was this an open random number table? 4. Inconsistency in number of losses drop outs reported in 2004 (2 in placebo group due to non compliance and 1 in flutamide group because she got pregnant) but not reported in 2006 (there only 1 in placebo group dropped out for non attendance and 3 in flutamide group because of increased transaminases), can you please explain? Resent 13-5-2013 Resent 2-6-2013		
Ganie 2004	aca433@yahoo.com, e-mail sent 10-5-2013 Dear professor Ammini, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. Journal of Clinical Endocrinology and Metabolism 2004;89(6):2756-62)	Not applicable	

Table 4. Contact with investigators (*Continued*)

	To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 2. There is inconsistency between the text and Figure 1 about the numbers that dropped out. Can you clarify how many dropped out in each group and for what reason? Thank you so much for your efforts Best regards Esther van Zuuren Resent 2-6-2013 Resent 29-6-2013 Reply 28-7-2013 The consecutive subjects were enrolled and assigned a code. One clinician would assign the code and the subsequent allocation would be done by the another. They were randomized on the basis of random number allocation which was computer generated. Neither the subjects nor the investigators could forsee the assigned group till OGTT was done. After that the study was open label Sorry there is discrepancy, as data is not clearly indicated. As indicated in Fig 1. Adverse events of numbers 4 versus 2 has inadvertently got transposed between metformin		

Table 4. Contact with investigators (*Continued*)

	and spironolactone arms.The details are as under: Spironolactone n=41 Polyurea =4 withdrew 1 Abdominal pain =1 withdrew 1 Menstrual irregularity= 9 withdrew 2 Lost to follow up =1 Incomplete data= 2 Total analysed =34 Metformin n=41 GI effects -Vomiting /nausea=4 withdrew=1 Diarrhea =8 withdrew =1 Hyeradrenergic symptoms= 2 Incomplete data =2 Lost to follow up=2 Total analysed= 35 29-7-2013: Dear professor Ganie, I did not receive your first mail, unfortunately. I still have some questions. The method to conceal the allocation **is still not clear** to me. It now looks like the investigator could see the code. I understand indeed from the paper that it was computer generated, but **how were the codes hidden for the investigators and the patients?** And the number in the metformin group are also not completely clear GI effects -Vomiting /nausea=4 withdrew=1 Diarrhea =8 withdrew =1 Hyeradrenergic symptoms= 2 withdrew???? Incomplete data =2 withdrew???? Lost to follow up=2 I suppose these were withdrawn Total analysed= 35 It now looks like 8 instead of 6 were withdrawn, please clarify?		
Ghosh 2008	Elsheikh Mohgah (Mohgah.Elsheikh@royalberkshire.nhs.	No	

Table 4. Contact with investigators (*Continued*)

	uk] e-mail sent 10-5-2013 Dear Dr Mohgah My colleagues and I are conducting a Cochrane Systematic Review Interventions for hirsutism excluding laser and photo epilation therapy and we have identified the study conducted by Ghosh D Murphy C and yourself. We note that the study was presented in Harrogate in 2008, can you please confirm if you have published the full study or if further trial conduct and data are available and you would be able to share these with us? Thanks you so much for your efforts Best regards Esther van Zuuren Reply 14-5-2013 Hello I'm afraid we only published the study in abstract form, presenting it at the British Endocrine Society meeting in 2008. Regards Mohgah Elsheikh		
Hamzavi 2007	18-5-2013 hlui@interchange.ubc.ca (sequence generation) reply 18-5 Thanks for your email and consideration of our article. Here is how we did the randomization. Prior to recruiting any of the subjects: 1. Coin toss. One toss for each patient to be recruited. 2. Record the successive results of each coin toss. 3. Put the result of the coin toss in successive numbered sealed envelopes. The coin toss result determined which side of	Yes	

Table 4. Contact with investigators (*Continued*)

	the face was randomized to receive the treatment cream in a blinded manner. 4. As each patient was enrolled, each successive envelope was opened.		
Ibáñez 2009	14-5-2013 'libanez@hsjdbcn.org' Could you provide us with data at 18 months for Ferriman-Gallwey scores for the two groups? (before they were subrandomised) The table below does not provide data for "met+ oestro progestagen + flu + pio group" and "met+ oestro progestagen + flu + placebo group", but already incorporated the subrandomisation afterwards. Could you provide us with data for testosterone, androstenedione, DHEAS and SHBG at 18 months for the original randomized groups? The baseline data are also somewhat different then in the 2008 paper. Not sure which are correct? Could you clarify? Response 14-5-2013 Dear Dr. van Zuuren, This was a double-blinded, placebo-controlled study. Accordingly, I did not know the identity of the patients until after the compeltion of the study I have searched through my files, and I hope that the results I provide are correct **met+ oestro progestagen + flu + pio group** **baseline at 18 months** **F&G score** 17.7 ± 1.0 9.5 ± 0.5 **Testosterone (ng/dL)** 55 ± 5 **D4-A (ng/dL)** 264 ± 15	Yes	

Table 4. Contact with investigators (*Continued*)

	DHEAS (ug/dL) 172 ± 14 **SHBG (nmol/L)** 170 ± 7 **met+ oestro progestagen + flu + placebo group** **F&G score** 16.4 ± 0.9 8.9 ± 0.5 **Testosterone (ng/dL)** 55 ± 4 **D4-A (ng/dL)** 287 ± 20 **DHEAS (ug/dL)** 213± 25 **SHBG (nmol/L)** 169 ± 7 **The baseline data are also somewhat different then in the 2008 paper. Not sure which are correct? Could you clarify?** I think that one of the women dropped out of the study, and we deleted her data		
Ibáñez 2012	14-5-2013 'libanez@hsjdbcn.org' We have another include in our Cochrane review on hirsutism "Ethinyl estradiol-cyproterone acetate versus low-dose pioglitazone-flutamide-metformin for adolescent girls with androgen excess: divergent effects on CD163, TWEAK receptor, ANGPTL4, and LEPTIN expression in subcutaneous adipose tissue. Journal of Clinical Endocrinology and Metabolism 2012;97(10):3630-8." (We have included otehr studies as well) Could you provide us with the data for Δ 0-12 months androstenedione in ng/dl and DHEAS in microgram/dl for both groups. Those miss in table 2 (and were available in the 2011 paper for 6 months) 19-5-2013 reply Here they are: D4-A: Diane: -111 +/- 32 PioFluMet: -109 +/- 38	Yes	

Table 4. Contact with investigators (*Continued*)

	DHEAS: Diane: -61 +/-19 PioFuMet: 13 +/- 13 EvZ had additional question if the data were with SEM or SD, seemed SD. Prof Ibáñez confirms SD		
Jackson 2007	mail sent 16-5 jcaro@caroresearch.com Dear professor Caro My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Jackson J, Caro JJ, Caro G, Garfield F, Huber F, Zhou W, et al. The effect of eflornithine 13.9% cream on the bother and discomfort due to hirsutism. International Journal of Dermatology 2007;46(9):976-81) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence. It states that it was a computer generated random list where even and odd numbers were allocated to the treatments. Was it on alternation? 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling partici-	Yes	

Table 4. Contact with investigators (*Continued*)

	pants could not foresee the upcoming assignment (this is not the same as blinding!!). 3. The numbers that started in each group? In the study of Wolf 2007, it also states 594, but the numbers add up to 496? 4. What was the method of blinding, how were patients and investigator blinded to treatment 5. What were the reasons for loss to follow-up? reply 17-5-2013 Dear Dr van Zuuren Thank you for contacting me about this. My involvement in these studies was limited to the design and implementation of the PRO component. Thus, I do not have the answers to your questions. I have passed them on, however, to Dr. Jackson who is now at Thomas Jefferson University. Hopefully, he will be able to respond. Best regards, Jaime 27-5-2013, asked for Jackson's mail address Hi I am copying him on your email. Joseph.Jackson@jefferson.edu Later 27-5-2013 Hi Esther, Sorry for the delay in getting back to you. I was away at a meeting in New Orleans. I have to follow up on this with former colleagues at BMS; I retired in 2010. I did discuss the matter with a colleague and we believe dynamic balancing was		

Table 4. Contact with investigators (*Continued*)

	used to balance the randomization across sites. I hope to have a more definitive soon. Let me know if this helps, Joe Dear Esther, I will need to discuss this with my statistical colleagues. I know that dynamic balancing was used across many trials in the Pharmaceutical Research Institute of BMS, and of course there were many filings with FDA, EMA... I'll get on this tomorrow as today is a holiday for us, Cheers, Joe 29- 5-2013 cc chensheng.lin@bms.com; kathyschrode@yahoo.com; jaime.caro@mcgill.ca; wenjiong. Zhou@unitedbiosource.com Dear Dr. van Zuuren, I have followed up with everyone on the cc list [2 statisticians (Drs. Zhou and Lin), the regulatory lead (Dr. Schrode) and Dr. Caro (The MD for the QOL work)] and have the following to report: 1. Below please find Dr. Zhou's summary concerning the randomization. 2. Dr. Schrode plans follow up with the company concerning other questions regarding hirsutism in women that could be answered by access to the final study report. 3. I believe that Dr. Schrode will follow up with you directly Hope this helps, Joe Hi Joe -		

Table 4. Contact with investigators (*Continued*)

	I dug out text portion of the final study report for the two pivotal studies (DE140-001 and DE140-002) **Here is the language for randomization -** Subjects were assigned treatment by a computer-generated randomization schedule restricted to ensure distribution of eflornithine 15% cream and its vehicle in a 2:1 ratio, respectively, within each investigational site Subjects were randomized to treatments with study medication on day two if qualified by the criteria of the protocol. Subject numbers and numbers identifying study medication containers corresponded directly. Subject numbers were assigned sequentially at each investigational site in strict numerical order as subjects were randomized [Wenjiong's comment -- So, this is simple randomization with 2:1 ratio, stratified by site. I don't believe the randomization schedule is an even and odd number alternating. Subject numbers were sequentially assigned within the site based on the timing of randomization within the site.] **Here is the language for blinding of study drug-** Blinding of the eflornithine 15% cream and its vehicle was assured by the fact that both study medications were packaged in identically appearing 15g plastic tubes bearing three-panel, two-part double-blind		

Table 4. Contact with investigators (*Continued*)

	labels. Labels affixed to the tubes (the only label to which subjects had access) contained no evidence of the identity of the contents. The second panel of the tear-off part of the label was a sealed envelope concealing the identity and lot number of the treatments. These tear-off portions were to be affixed to the subjects CRFs and opened only in the case of a medical emergency in which the investigator had determined that the information was absolutely necessary, i.e., that it would alter the subjects immediate management. Eflornithine 15% cream and its vehicle were matching cream formulations and it was not considered possible to differentiate one treatment from the other solely by tactile or visual evaluation The protocol for this study specified that dispensing of study medications at the investigational site was to be done by a staff member who was not responsible for conducting any of the clinical evaluations. Therefore, the chances of the investigator equating a particular level of response with what he/she considered to be a particular treatment was minimal So above should suffice questions #1, #2, and #4. For question #5. I don't see a reason further specified for "lost to follow-up". Don't recall or have CRF, I have a feeling that "lost to follow-up" is just a simple check-box without further specification		

Table 4. Contact with investigators (*Continued*)

	For question #3. 594 seems to be referring to total number of treated patients in both studies (287 for DE140-001 and 307 for DE140-002). I don't know what 496 is referring to. I don't have the paper That is all I can do. Hope that helps. Thanks, Wenjiong 24-12-2013 jaime. caro@mcgill.ca Dear professor Caro, We are conducting a Cochrane review on interventions for hirsutism, and we would like to have the information on Caro JJ, Caro G, O'Brien JA, *et al.* Assessing quality of life implication of depigmentation: the BASC scale. Which was presented at the 54th Annual meeting of the American Academy of Dermatology 1996 10-15 Feb in Washington Can you provide me with a scanned copy, or an abstract? I need the full author string as well as poster number. Our university Library has no access to it, and the AAD could not help me anymore with this. I looked everywhere on the web without success I would appreciate it enormously if you could help me Reply: Thank you for contacting me about this. I will ask my assistant to see if she can find a copy but it is quite unlikely given that it is nearly 18 years ago. All of that has long ago been sent to off-site storage or destroyed. The application to		

Table 4. Contact with investigators (*Continued*)

	hirsutism was published later, however, as 'The effect of eflornithine 13.9% cream on the bother and discomfort due to hirsutism. International Journal of Dermatology 2007;46(9) :976-81)' 24-12-2013: Yes we have that study included, but the link of the reference is not working to leads to the abstract of the Annual meeting. As we need to refer to the original source of the instrument, we need to have the details of that abstract. So I hope your assistant can find it and send me it 09-01-2014. Both Prof Caro, as well as the AAD could not provide us with the abstract on the BASC scale		
Kriplani 2009	Email: kriplanialka@gmail.com (concealment) 30-12-2013 Resent 12-5-2014. No response	Not applicable	
Kriplani 2010	Email: kriplanialka@gmail.com (concealment) 20-5-2013 Resent 2-6-2013, 29-6-2013. No response	Not applicable	
Lakryc 2003	edmund@baracat.com.br and jsoares415@hotmail.com e-mail sent 20-5-2013 Dear professor Baracat My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies for which you are corresponding author, have been identified as potentially eligible for inclusion (The benefits of finasteride for hirsute women with polycystic ovary syndrome or idiopathic	Yes	

Table 4. Contact with investigators (*Continued*)

	hirsutism. Gynecological Endocrinology 2003;17(1):57-63.) I have copied professor Soares in the mail as I was not sure if the e-mail address was correct To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. There were 10 drop-outs, how many in each treatment arm? 2. What were the specific measures used to blind participants from knowledge of which intervention a participant received (how was the blinding done)? The blinding of the personnel is clear. Thank your for your time and efforts Best regards Esther van Zuuren reply 20-5-2013 I and Prof Baracat are pleased with your e-mail. The answers for your questions are above: 1) 10 drop-outs: 6 for placebo group and 4 for finasteride group 2) The capsule of placebo was similar to the one of finasteride and the flask had only identification of XY (placebo) or YX (finasteride). The physicians and patients were blind to this information. After the end of this study, both physicians and patients were informed on the groups. Also, we did not permit a direct conduct the patients during the study. If you have any questions, please contact me. Best regards,		

Table 4. Contact with investigators (*Continued*)

	José Maria Soares Jr Edmund C Baracat		
Le Donne 2012	e-mail sent 21-5-2013 mariale-donne@tin.it Dear professor Le Donne My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Le Donne M, Alibrandi A, Giarrusso R, Lo Monaco I, Muraca U. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition [Dieta, Metformina e Inositolo in Donne Sovrappeso e Obese Con Sindrome Dell'Ovaio Policistico: Effetti Sulla Composizione Corporea]. Minerva Ginecologica 2012;64 (1):23-9) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence. It states that it was a computer generated random list where even and odd numbers were allocated to the treatments. Was it on alternation? 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!).	Yes	

Table 4. Contact with investigators (*Continued*)

	Thank you so much for your efforts. Reply 30-5-2013 Thank you for your interest about my publication "Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition" 1. The method used to generate the allocation sequence, was a computer generated random list where even and odd numbers were allocated to the treatments.It was on alternation. 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment. It is the same as blinding. Best regards Maria Le Donne Our response: Dear professor Le Donne, Thank you for your additional information. Allocation concealment is not the same as blinding, therefore we added that information that it is not the same, examples of adequate methods of allocation concealment are e.g. include sequentially numbered, opaque, sealed envelopes (SNOSE); sequentially numbered containers; pharmacy controlled randomization; and central randomization Blinding is about procedures		

Table 4. Contact with investigators (*Continued*)

	that prevent study participants, caregivers, or outcome assessors from knowing which intervention was received (e.g same tablets, same package, smeel, taste) As your study has been randomised based on alternation it is not truly randomised but quasirandomised, and therefore unfortunately we will not be able to include this study Just for my understanding, why did you use a computer generated random list when it was on alternation for odd/even numbers? You don't need a computer for alternation, do you? Response Zbys:Dear Dr Le donne Alternate allocation by odd and even number is not a method of true randomization. True randomization ensures that every participant has an equal opportunity to receive one or other intervention by chance alone. This cannot be said to apply to alternation ie odd even allocation. Regarding allocation concealment and blinding... these are not the same and dont share the same potential to adversely affect ie bias the outcome. Allocation concealment is always possible whereas blinding may not and refers to the period prior to the administration of the interventions whereas blinding occurs or doesnt occur at the actual time of the administration of the intervention. Your perception of these as being identical is quite commonly held but regrettably is incorrect.		

Table 4. Contact with investigators (*Continued*)

	There is quite an extensive literature on this which I would be happy to provide. The impact of inadequate allocation concealment on the effect estimate is far greater than that of blinding, and consequently of significant importance. Thank you for the information you have provided it has enable us to clarify aspects of your study which have a potential impact on the conclusions that can be drawn I do hope you find this helpful? 2-6-2013: sent additional mail as I think she gave confusing reply Dear professor le Donne,I am wondering before I exclude your study, if you are sure it was computer generated AND on alternation as this does not make sense. If it has been computer generated I cannot see how it would be on alternation, so can you please confirm it it was on alternation? I think you might have been confused? Resent 9-6-2013 Resent 29-6-2013 Reply 30-6-2013 Yes I was confused, I confirm that it was on alternation Best regards Maria Le Donne		
Lello 2008	e-mail sent 21-5-2013 lellostefano@libero.it Dear professor Lello My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as	Not applicable	

Table 4. Contact with investigators (*Continued*)

	potentially eligible for inclusion (Effects of two estroprogestins containing ethynilestradiol 30 microg and drospirenone 3 mg and ethynilestradiol 30 microg and chlormadinone 2 mg on skin and hormonal hyperandrogenic manifestations. Gynecological Endocrinology 2008;24 (12):718-23.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence. It states that it was a computer generated random list where even and odd numbers were allocated to the treatments. Was it on alternation? 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). Thank you so much for your efforts. Best regards Esther van Zuuren Resent 2-6-2013 Resent 29-6-2013		
Maciel 2004	e-mail sent 27-5-2013 ecbaracat@gmail.com, garmaciel@gmail.com, jsoares415@hotmail.com Dear professor Baracat, you and professor Soarez Jr have been very helpful with the other study, so I hope you can help with this one as well	Yes	

Table 4. Contact with investigators (*Continued*)

	(Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. Fertility and Sterility 2004;81(2): 355-60. The study is very well designed, but I only have one extra question How many dropped exactly out from each group, it says 5/34, how many from each group and for which reason in each group? Thank you so much again for your efforts Best regards Esther van Zuuren Reply 27-5-2013 Dear Dr van Zuuren, I talked with Dr Gustavo Maciel about your question. He will check the data for answering your question. If you have any difficult with Dr Maciel response, please, contact me. Best regards, José Maria Dear prof Zuuren It is a pleasure for us to collaborate in your research. kind regards Edmund C Baracat, MD, PhD Professor and Head Gynecology Division University of Sao Paulo Medical School 6-6-2013 Dear Dr Esther, we reviewed our records and identified the reasons the subjects dropped out the study: pregnancy (n=2): one of the PCOS group and one of the control; both were nonobese; unknown reason (n=2): two from the control group, both		

Table 4. Contact with investigators (*Continued*)

	obese. diarrhea (n=1): PCOS obese I hope the information will be useful. Our best regards Gustavo		
Madani 2012	e-mail 9-6-2013 ashrafim@royaninstitute.org Dear professor Ashrafi, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Madani T, Irani S, Ashrafi M, Nabavi M.A. The effect of flutamide on ovulation induction in PCOS patients. International Journal of Fertility and Sterility 2012;6(1):65-70.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence. It states that it was a computer generated random list where even and odd numbers were allocated to the treatments. Was it on alternation? 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not	Yes	Quasi-randomised so an exclude

Table 4. Contact with investigators (*Continued*)

	the same as blinding!!). 3. How was grade 1 and grade 2 defined? What were the cut-off points? 4. What were the baseline values for hirsutism, I only see the values after first and second cycle? 5. What were the values of testosterone after the 2 cycles for both groups? 6. What was the mean BMI (SE) for both treatment groups after 2 months? Resent 29-6-2013 Resent 06-07-2013 Resent 11-7-2013 Reply 20-7-2013 Dear professor Zuuren Many thanks to your interest. To answer your questions we can explain in this manner: 1- The method we used was on alternation 2- It was a blind study and neither participants nor investigators could fore see the treatment. 3- According to ferrimann-Gall way classification there are four grade but for simplify we considered the grade I,II as hypohirsutism(grade I in our study) and grade III , IV we considered as hyperhirsutism(grade II in our study) 4- In the beginning of the study hirsutism was assessed. 5- Testestron wasn't measured at the end of the study because it wasn't the main aim of the study. 6- Regarding to BMI, No changed was seen.		

Table 4. Contact with investigators (*Continued*)

Mastorakos 2002	9-6-2013 mastorak@mail.kapatel.gr incorrect, then mastorakg@ath.forthnet.gr Dear professor Mastorakos, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertility and Sterility 2002;77(5):919-27) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence. 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 3. Where there no drop-outs? 4. Are these adolescents also part of the 2006 paper (Fertility and Sterility 2006;85(2): 420-7)? Resent:11-07-2013 Resent 26-7-2013 Reply 29-7-2013 1. No all numbers generated (odds and even) were randomly	Yes	

Table 4. Contact with investigators (*Continued*)

	given and not on alternation. 2. If question #2 is not responded by the random allocation of numbers then, I am not sure I understand the meaning of question #2. I would greatly appreciate if you could be more specific. 3. No drop-outs 4.I responded to this in my previous email (see study below) Reply by EVZ: explanation of allocation concealment Reply 29-7-2013: Thank you for the analytical explanation of concealment of allocation. In our everyday clinical research practice we considered this procedure as part of the whole randomaization. The randomization is performed by our computer technicien who generates the random numbers and he is the only one to know in each study the allocation sequence until the moment of assignment Thanks again for your informative intervention Reply evz sent paper Altman-Schulz		
Mastorakos 2006	mastorakg@ath.forthnet.gr Dear professor Mastorakos, As said in my former mail, my colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Mastorakos G, Koliopoulos C, Deligeoroglou E, Diamanti-Kandarakis E, Creatsas G. Effects of two forms of combined oral contraceptives on carbohydrate metabolism in adoles-	Yes	

Table 4. Contact with investigators (*Continued*)

	cents with polycystic ovary syndrome. Fertility and Sterility 2006;85(2):420-7.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 2. Are these adolescents also part of the 2002 paper (Fertility and Sterility 2002;77(5): 919-27)? 3. Can you provide us with the data on the Ferriman- Gallwey score and the androgen levels after 12 months 12-6-2013 Dear Professor van Zuuren Thank you for your interest to our work. I am out of town till the 21st. I will be happy to respond then 29-6-2013 Dear Professor Mastorakos, Have you already time to look at the two e-mails I sent you on the two studies? Resent 11-7-2013 Resent 26-7-2013 Reply 29-7-2013 1. I believe this question regards the randomness of the assignment cause this is not reported in our paper. In all our studies we employ randomly generated numbers from the appropriate softwares.		

Table 4. Contact with investigators (*Continued*)

	2. No. In fact we repeated the same study because all the material collected from the first study had been utilized. 3. I ll try to do so. I have to check with Dr. Caroline Koliopoulos cause this study was part of her thesis and I will come back ASAP Reply by EvZ Regarding 1, it is about concealment, not about the sequence generation. So how was the randomisation sequence kept secret to investigator and patients? Which method of concealment was used Regarding 2. OK other adolescents 3, we wait then Resent 8-8-2013 9-8-2013 Dear Esther I am sending you the data requested for the 2006 paper as prepared by my co-author Dr. C. Koliopoulos Thank you for having requested them. Hope you find it useful I remain at your disposal for any further clarification. I will be out of town till august the 26th. Wish you happy summer vacation		
Moghetti 2000	paolo.moghetti@univr.it 17-6-2013 My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, Perrone F, et al. Comparison of spironolac-	Yes	

Table 4. Contact with investigators (*Continued*)

	tone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism 2000;85 (1):89-94.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence 2. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) 3. Baseline values and end of treatment values for total testosterone and androstenedione Thank you so much for your efforts. Resent 29-6-2013 Reply 28-7-2013 1: The allocation sequence was obtained by randomly generated numbers 2:A person, not involved in the study and working in the hospital pharmacy, prepared a series of identical wafer capsules containing the different drugs or placebo, in numbered packets. The packets were assigned progressively to the recruited participants. The capsule content corresponding to the sequence of the numbers remained unknown to the researchers until the end of the study, and measurements of both hirsutism		

Table 4. Contact with investigators (*Continued*)

	score and hair diameter were blinded to the treatment group 3. Baseline and end of treatment values (nmol/L, mean, SD) for total testosterone and androstenedione in the 4 treatment groups were respectively the following: Total testosterone Spironolactone 2.06+0.69 and 2.04+0.47 Flutamide 1.78+0.65 and 1.73+0.31 Finasteride 2.15+0.56 and 2.71+0.51 Placebo: 1.76+0.51 and 1.86+0.47 Androstenedione Spironolactone 13.5+7.3 and 14.7+7.1 Flutamide 15.3+5.6 and 12.6+4.4 Finasteride 16.6+3.5 and 18.3+4.3 Placebo: 15.0+5.1 and 16.4+5.6 Reply by EvZ 30-7-2013: Thank you for your reply. Everything is clear except the method of how the numbers were generated at random, as there are several methods. Of course the numbers are generated at random, otherwise it would not have been a randomised controlled trial, but how were the numbers generated at random? Reply 30-7-2013 The numbers were generated by a computer.		
Moghetti 2000B	paolo.moghetti@univr.it 18-6-2013 Dear professor Moghetti, Yesterday I already sent you an e-mail about one of your studies in hirsute women, today I have questions about another study of yours	Yes	

Table 4. Contact with investigators (*Continued*)

	My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and another of your studies have been identified as potentially eligible for inclusion (Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. Journal of Clinical Endocrinology and Metabolism 2000;85 (1):139-46.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. how many were randomised to each group in protocol A? 2. the method used to generate the allocation sequence 3. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) 4. What were mean baseline values of hirsutism score and what were the mean end values at 6 months in protocol A Thank you so much for your efforts. Resent 29-6-2013 Reply 29-6-2013		

Table 4. Contact with investigators (*Continued*)

	Dear Dr. van Zuuren, Thank you for your interest in my studies. I am out of work in these days and it is not easy for me to answer your questions immediately. However, I will do all my best to reply asap. Best regards Paolo Moghetti Resent 11-7-2013, he is away until 20-7 Reply 28-7-2013 1. The number of subjects randomized in the double-blind, placebo-controlled trial (protocol A) was 12 in the metformin group and 11 in the placebo group 2.The allocation sequence was obtained by randomly generated numbers 3.A person, not involved in the study and working in the hospital pharmacy, prepared a series of identical wafer capsules containing the different drugs or placebo, in numbered packets. The packets were assigned progressively to the recruited participants. The capsule content corresponding to the sequence of the numbers remained unknown to the researchers until the end of the study, and measurements of both hirsutism score and hair diameter were blinded to the treatment group 4. The baseline and end of treatment hirsutism scores (mean, SD) of subjects included in protocol A were respectively the following: Metformin: 8.9±5.5 and 9.6±5.1 Placebo: 12.7±3.8 and 14.5±6.2		

Table 4. Contact with investigators (*Continued*)

	It should be noted that hirsutism was not a predefined outcome in this study and PCOS women were not recruited according to the presence of hirsutism		
Morin-Papunen 2000	21-6-2013 juha.tapanainen@oulu.fi, laure.morin-papunen@oulu.fi Dear professor Morin-Papunen, and professor Tapanainen, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and another of your studies have been identified as potentially eligible for inclusion (Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. Journal of Clinical Endocrinology and Metabolism 2000;85 (9):3161-8.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. how many were randomised were originally randomised to each group (it is clear how many finished 3 and 6 months, but not how many started in each group)? 2. the method used to generate the allocation sequence 3. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been**	Yes	

Table 4. Contact with investigators (*Continued*)

	foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) Reply 20-6-2013 Dear doctor van Zuuren, Thank you for your mail. I try to answer to your questions. 1. how many were randomised were originally randomised to each group (it is clear how many finished 3 and 6 months, but not how many started in each group)? Five more patients wer randomised,3 in the metformin group and 2 in the DN group. Three of them were dropped because of discovered T2DM (2 in the met group and 1 in the DN group), and 2 (one in each group) did not want to participate for personal reasons 2. the method used to generate the allocation sequence: it was performed by the hospital pharmacy with 1:1 allocation in random blocks of ten using two computer-generated lists 3. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!): the allocation was concealed in a closed envelope where the number of the patient was written. The participant knew the allocation after she had accepted to participate In this study, no blinding was		

Table 4. Contact with investigators (*Continued*)

	possible nor done. I hope that this helps you! Best regards Laure Morin-Papunen		
Morin-Papunen 2003	21-6-2013 laure.morin-papunen@oulu.fi Dear professor Morin-Papunen, We have also 2 questions about your study "Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. Journal of Clinical Endocrinology and Metabolism 2003;88 (1):148-56" 1. the method used to generate the allocation sequence 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) 29-10-2013 Dear professor Morin-Papunen, I am not sure if you have seen these questions on another study of yours (see below). The answers to the other study were really helpful Best regards Esther van Zuuren 30-6-2013 Dear professor van Zuuren, I am sorry to be so late with my answer. I was on holidays last week and had no access at my	Yes	

Table 4. Contact with investigators (*Continued*)

	mail The sudy on nonobese women was done exactly as the previous one on obese, ie the answers to your questions are the same as in the previous study. I hope that this helps you, do not hesitate too ask more if needed Best regards Laure		
Navali 2012	27-6-2013 mashrabi1383@yahoo.com; parvinbastani@yahoo.com Dear professor Mashrabi My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and another of your studies have been identified as potentially eligible for inclusion (Navali N, Shokoufe LA, Mallah F, Bastani P, Mashrabi O. Comparing therapeutic effects of metformin and pioglitazone in polycystic ovary syndrome (PCOS). Pakistan Journal of Medical Sciences 2012;28(3):390-4) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence 2. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) Thank you so much for your efforts.	Not applicable	

Table 4. Contact with investigators (*Continued*)

	Resent 06-07-2013 Resent 24-07-2013		
Önalan 2005	Email: gogsenonalan@yahoo.com (sequence generation, concealment, blinding) 27-6-2013 Resent 06-07-2013, 24-07-2013. No response	Not applicable	
Oner 2011B	Email: onerg@yahoo.com (sequence generation, concealment) 27-6-2013 Resent 06-07-2013, 23-07-2013, 8-8-2013. No response	Not applicable	
Ortega 2005 and 2005B	ortegacarlos@hotmail.com 1-7-2013 Dear professor Ortega-González, My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and two of your studies have been identified as potentially eligible for inclusion (Ortega-González C, Cardoza L, Coutiño B, Hidalgo R, Arteaga-Troncoso G, Parra A. Insulin sensitizing drugs increase the endogenous dopaminergic tone in obese insulin-resistant women with polycystic ovary syndrome. Journal of Endocrinology 2005;184(1):233-9. and Ortega-González C, Luna S, Hernández L, Crespo G, Aguayo P, Arteaga-Troncoso G, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. Journal of Clinical Endocrinology and	Yes	Copub so 2005B removed from included studies

Table 4. Contact with investigators (*Continued*)

	Metabolism 2005;90(3):1360-5.) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following information: 1. Is the same study population involved in both studies? As I don't see any referring to each of the papers, but study design is the same and only difference in total number of 3 participants Reply 2-7-2013 Dear Dr. E.J.van Zuuren: I appreciate your interest in our research. This is effectively the same cohort of patients Originally we recruit 57 patients, of which, 10 were lost to follow up (5 in each group), 5 were excluded for presenting gastrointestinal side effects (all of them belonged to the group treated with metformin), and 8 were pregnant (5 from group treated with pioglitazone, 2 in the first half of the study and 3 in the second half, while 3 pregnant patients were assigned to group management with metformin). At the end were 34 women (17 in each group) to which they do metoclopramide protocol to assess dopaminergic tone The difference between the two studies, it is basically for work published in J Clin Endocrinol Metab we do not include a 5 women lost to follow up, very early in the study (two women in the pioglitazone group and three women in the metformin group) and for the analysis of the study published in J Endocrinology, a woman who presented severe gastrointestinal ef-		

Table 4. Contact with investigators (*Continued*)

	fects towards the end of study in the metformin group did not authorize the second test with metoclopramide, so it was excluded from the final analysis Hence the difference between the *"n"* of both studies. I hope this information will be useful to you and your group of researchers		
Otta 2010	05-07-2013 endofux@yahoo.com.ar Dear professor Otta, My colleagues and I are conducting a Cochrane review ((Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Otta CF, Wior M, Iraci GS, Kaplan R, Torres D, Gaido MI, Wyse EP. Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. Gynecological Endocrinology 2010;26 (3):173-8) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) 2. The method used to blind	Yes	

Table 4. Contact with investigators (*Continued*)

	participants and investigators from knowledge of which intervention a participant received Resent 23-07-2013 Resent 8-8-2013 Reply 8-8-2013 Dear Dr van Zuuren I give you my apologies for not answering your first mail. I have sent your questions to the person who was responsable of the randomization of my trial. As soon as he answer, I will mail it to you. I thank your consideration to choose my trial for your meta analysis. Sincerely Fux Otta, Carolina Reply 18-8-2013 1- Simple random was used to allocate patients to treatment or placebo 2 - Each pack (en vez de sachet) of treatment was opaque and coded from the laboratory. We guarantee the double blinding because neither patients nor us knew which treatment they were allocated; nor could we find out because that was done from the laboratory. Blinding was opened at the end of the study of 30 patients. The laboratory sends us a letter with the codes 19-8-2013 Pills were exactly the same in shape and colour, and both (metformin and placebo) were tapered to one and a half pill BID Package codes were generated by random program from the laboratory		
Sabuncu 2003	Email: sabuncu@ixir.com and tsabuncu@harrou.edu.tr (both addresses are no longer in use)	Not applicable	

Table 4. Contact with investigators (*Continued*)

	and no recent one available. (concealment, blinding) 11-7-2013		
Sert 2003	e-mail 13-7-2013 muratser@mail.cu.edu.tr Dear professor Sert My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Sert M, Tetiker T, Kirim S. Comparison of the efficiency of anti-androgenic regimens consisting of spironolactone, Diane 35, and cyproterone acetate in hirsutism. Acta Medica Okayama 2003;57(2):73-6. [PubMed: 12866746] To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence, as it does not seem to be randomized (people that came first period came in group 1, people in second months in group 2 and people in 3 months in group 3) ? 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). Thank you so much for your efforts. Reply 14-7-2013 Dear E.J.van Zuuren, MD	Yes	It is a CCT

Table 4. Contact with investigators (*Continued*)

	I have just seen your e-mail. I thank you for interesting our study. Regarding with the study; 1. Inclusion of the patients were done by randomly and sequentialy their appliance to our outpatient clinic at the determined period (one month for each group). So, the inclusion method for the 3 groups were similar 2. In this study, study subjects did not know the comparement of the different therapy groups with each other. They informed about whether their treatment were efficious or not with respect to their basal findings and complaints (the same for 3 groups). And, investigator who evaluated the Ferriman score did not know the study patients (he had been performing routin all outpatient subjects who were also not included the study I hope this explanation will help you. With my best regards, Prof. Dr. Murat Sert		
Smith 2006	e-mail 13-7-2013 ssmith@therapeuticsresearch.com; ssmith@stacyrsmithmd.com Dear professor Smith, My colleagues and I are conducting a Cochrane review ((Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Smith SR, Piacquadio DJ, Beger B, Littler C. Eflornithine cream combined with laser therapy in the management of unwanted facial hair growth	Yes	

Table 4. Contact with investigators (*Continued*)

	in women: a randomized trial. Dermatologic Surgery 2006;32 (10):1237-43).To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 2. The method used to blind participants and investigators from knowledge of which intervention a participant received Best regards Esther van Zuuren Reply 22-7-2013 Dr. van Zuuren, With respect to your inquiries: - The treatment allocation sequence was predetermined using a coputer-generated randomization sequence. Prior to the start of the study, the medication container assignments for EACH subject number were placed into sealed envelopes marked with subject numbers. As each new subject was enrolled, the next highest number was assigned and at the time of randomization, the envelope was opened which instructed the site staff to dispense certain containers of study medication. The study medication containers did NOT reveal whether the product inside was active or		

Table 4. Contact with investigators (*Continued*)

	placebo and the numbers were different for each study container. The actual treatmant assignements were maintained by an off-site study administator not directly related to the site thus the site did not have regular access to the treatment assignments and could only obtain that information through a formal unblinding process. - Participants (via the staff) received medication containers that contained either the active medication or a placebo vehicle prepared by the medication manufacturer that matched the active product in color, feel and odor. Please let me know if you need further details or clarification		
Taheripanah 2010	Taheri-panah@sbmu.ac.ir e-mail 14-7-2013 **(e-mail address is not correct anymore) Can't find a more recent one, and I cannot find recent e-mail address of any of the other authors** Dear Professor Taheripanah My colleagues and I are conducting a Cochrane review (Interventions for hirsutism excluding laser and photoepilation therapy) and one of your studies have been identified as potentially eligible for inclusion (Taheripanah R, Sepahvandi M, Entezari A, Amiri Z, Neisani Samani E. Evaluation of serum PSA after cyproterone compound treatment compared with oral contraceptive pill in hirsute polycystic ovary syndrome patients. Middle East Fertility Society Journal 2010;15(3):159-62) To enable us to further assess this trial for inclusion I would	Not applicable	

Table 4. Contact with investigators (*Continued*)

	be obliged if you could you kindly provide us with the following missing trial details: 1.the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) 2. What was the first OCP (ingredients/brandname)? 3. Were there no drop-outs? 4. Are data presented with SD or SEM? 5. What were the units of DHEAS? (free testosterone was ng/ml) Thank you so much for your efforts.		
Tartagni 2000 and 2004	Email: m.tartagni@gynecology3.uniba.it (concealment, blinding) 27-7-2013 Resent 8-8-2013, 25-08-2013. No response	Not applicable	
Vigorito 2007	Email: francescoorio@virgilio.it (Sequence generation, concealment) 2-8-2013 Resent 8-8-2013. Reply 8-8-2013. No further response.	No	
Visnovský 2010	Email: visnovsky@jfmed.uniba.sk (sequence generation, concealment) 8-8-2010 Resent 25-08-2013. No response	No	
Zheng 2005	Email: dcotorzheng52@yahoo.com.cn, e-mail incorrect, no other contact. (sequence generation, concealment)	Not applicable	

Table 4. Contact with investigators (*Continued*)

	9-8-2013. No response		

Table 5. Overview of published reviews and guidelines

Study ID	Type of publication	Systematic search	Critical appraisal	Quality of evidence	Comments
Azziz 2003	Narrative review	No	No	Not assessed	**Conclusions:** "Treatment should be undertaken using combination therapy, to possibly include 1) hormonal suppression (oral contraceptives, long-acting gonadotropin releasing hormone analogues, and insulin sensitizers), 2) peripheral androgen blockade (spironolactone, flutamide, cyproterone acetate, or finasteride), and 3) mechanical/cosmetic amelioration and destruction of the unwanted hairs (electrology and, potentially, laser hair removal). Eflornithine hydrochloride 13.9% topical cream may also be useful to ameliorate unwanted facial hair growth"
Bailey 2014	NHS Question & Answer Only addressed efficacy of metformin	No	No	Not assessed	**Conclusions:** "Metformin has shown limited efficacy in PCOS symptoms of hirsutism (dose 1.5-2.0g/day) and acne (dose 1.

Table 5. Overview of published reviews and guidelines (*Continued*)

					5g/day), but further studies would be required to determine whether metformin has any real clinical benefits with regard to these symptoms."
Blume-Peytavi 2008	Narrative review Broad overview with recommendations for treatment supported by trials and systematic reviews if available	No	No	Not assessed	**Conclusions:** "For the majority of women, a monotherapy with oral contraceptives that have antiandrogenic activity is recommended as a first-line treatment for hirsutism. Combining an oral contraceptive pill with an antiandrogen is recommended if clinical improvement of hirsutism is insufficient after 6-9 months' monotherapy. In women who present with hirsutism, hyperandrogenism, and insulin resistance, insulin sensitizers are effective for the hirsutism as well as the hyperinsulinaemia, hyperandrogenism, and infertility but there is no convincing evidence that they are effective for hirsutism alone. Topical eflornithine is a medical therapy that can be a useful adju-

Table 5. Overview of published reviews and guidelines (*Continued*)

					vant for hirsutism when used in conjunction with systemic medications or with laser/photoepilation“
Blume-Peytavi 2011	Narrative review Short overview on unwanted hair growth and hypertrichosis	No	No	Not assessed	**Conclusions:** ”holistic treatment approach including evaluation of the implementation of emotional coping strategies and on-going support, lifestyle modifications, pharmacological interventions (to address underlying pathologies) and the use of cos- metic hair removal methods as either a stand-alone or adjunct treatment as appropriate to the individual.“
Blume-Peytavi 2013	Narrative review Broad review on diag- nosis and treatment of women with excessive hair including hypertrichosis	No	No	Not assessed	**Conclusions:** ”Because excessive hair growth in women may cause psychological and psychosocial problems, a holistic treatment approach, including support and emotional coping strategies, should be recommended.“ and ”treatment options, ...range from pharmaceuticals, including anti-androgens, enzyme inhibitors, and insulin-sensitizing agent to various

Table 5. Overview of published reviews and guidelines (*Continued*)

					physical and chemical epilation methods as well as laser hair removal. Monotherapie with OCPs that have an androgenic activity is usually first choice. Especially if quick improvement is desired, pharmaceutical treatment can be combined with epilation method of preference.“
Brodell 2010	Narrative review Review of hirsutism on the aetiologies, clinical features, approach to diagnostic evaluation, and treatment options	No, PubMed from 1981 and reference lists from review articles on hirsutism	No	Not assessed	**Conclusions:** ”A variety of treatments exist to help minimize the appearance of unwanted hair. “ OCPs, spironolactone, finasteride, metformin, eflornithine hydrochloride, photoepilation, and physical epilation are discussed
Castelo-Branco 2010	Narrative review General overview of hirsutism treatment options, supported by trials and meta-analyses or systematic reviews if available	No	No	Not assessed	**Conclusions:** ”Hirsutism can be effectively treated in many women by combining a non-pharmacologic method of hair removal and an OCP in women who not wish to become pregnant... If there is no improvement in 6 months, antiandrogen treatment may be added to the OC. Some clinicians prefer to

Table 5. Overview of published reviews and guidelines (*Continued*)

					initiate therapy with a combination of OC plus antiandrogens. Women with PCOS have other issues that require attention, including menstrual dysfunction, anovulatory infertility, and an increased risk of type 2 diabetes and other metabolic disorders. In this case, insulin lowering agents may be considered. Women who wish to become pregnant should not initiate pharmacologic therapy for hirsutism"
Cosma 2008	Systematic review and meta-analysis of RCTs of metformin or thiazolidinediones for the treatment of hirsutism	Yes MEDLINE, EMBASE, and Cochrane CENTRAL (up to May 2006)	Yes, well done, not fully reported	GRADE	**Conclusions:** "Imprecise and inconsistent evidence of low to very low quality suggests that insulin sensitizers provide limited or no important benefit for women with hirsutism." "The accompanying clinical practice guidelines, based on the evidence from this review along with the values, preferences, and expertise of the Task Force members, provide clinicians and patients with current recommendations"
Domecq 2013	Systematic review and meta-analysis of RCTs of lifestyle modifi-	Yes Ovid MEDLINE, OVID EMBASE, OVID *The*	Yes, well done	GRADE	**Conclusions:** "We found no significant effect of LSM on

Table 5. Overview of published reviews and guidelines (*Continued*)

	cation (LSM) programmes in PCOS	*Cochrane Library*, Web of Science, Scopus, PsycINFO, and CINAHL (up to January 2011)			pregnancy rate, and the effect on hirsutism was unclear."
Du 2012	Meta-analysis Meta-analysis of RCTs on effects of thiazolidinediones versus placebo on PCOS	MEDLINE, EMBASE, and *The Cochrane Library* up to June 2012	Yes (PRISMA)	Not assessed	**Conclusions:** "The effects of thiazolidinediones on the F-G score were not significantly different from placebo"
Du 2012b	Systematic review Systematic review and meta-analysis of RCTs comparing pioglitazone versus metformin in the treatment of PCOS	MEDLINE, EMBASE, China National Knowledge Infrastructure, and WANFANG DATA up to November 2011	In part based on PRISMA	Not assessed	**Conclusions:** "The meta-analysis revealed that the effect of pioglitazone on Ferriman-Gallwey scores was not significantly different from that of metformin". No reporting on effectiveness on hirsutism
Escobar-Morreale 2010	Narrative review: diagnosis and management of hirsutism	No	No	Not assessed	**Conclusions:** "Treatment must consider not only amelioration of hirsutism but also treatment of the underlying etiology and of any metabolic associations. When caused by a functional disorder, treatment of hirsutism should be chronic and should include cosmetic as well as interventions such as oral contraceptives and antiandrogens. For nonfunctional disorders, treatment should focus on

Table 5. Overview of published reviews and guidelines (*Continued*)

					solving the underlying etiology as hirsutism is usually responsive to the elimination of the source of androgen excess."
Escobar-Morreale 2012	Systematic review A systematic review and critical assessment of the available evidence pertaining to the epidemiology, pathophysiology, diagnosis, and management of hirsutism: a consensus statement by the Androgen Excess and PCOS Society. Broad overview with recommendations for treatment supported by trials	Reviews of published peer-reviewed medical literature identified studies evaluating hirsutism. Multiple databases were searched, including MEDLINE, EMBASE, Cochrane, ERIC, EBSCO, dissertation abstracts, and Current Contents	The committee critiqued each review before submitting the manuscript to the Androgen Excess-PCOS Society Board for approval. Incomplete reporting of assessments only blinding	Although the paper refers to GRADE, there is a lack of a clear transition from GRADEing the quality of evidence to recommendations	**Conclusions:** "Following evidence-based diagnostic and treatment strategies that address not only the amelioration of hirsutism but also the treatment of the underlying etiology is essential for the proper management of affected women, especially considering that hirsutism". "we recommend prescribing a low-dose neutral or antiandrogenic OCP as first-line therapy for hirsutism...we recommend prescribing an antiandrogen combined with OCPs in women presenting with moderate or severe hirsutism, or in those with a milder hirsutism who do not reach a satisfactory control of hair growth using OCPs alone after 1 year of treatment...we recommend against the use of metformin or other insulin sensitizers as therapy for

Table 5. Overview of published reviews and guidelines (*Continued*)

					hirsutism as its possible effects are unconvincing and possibly not superior to placebo.. ....We therefore recommend against the use of glucocorticoids, ketoconazole and GnRH analogues for first-line therapy of hirsutism because their effects are generally limited. In addition, other drugs are safer and/or more cost-effective.“
Guerra-Tapia 2011	Narrative review Review on effects of ethinyl estradiol/ chlormadinone acetate for the treatment of dermatological disorders under the control of androgens	No	No	Not assessed	**Conclusions:** ”In addition, in trials investigating the contraceptive efficacy of EE/ CMA, limited data suggest that there were also improvements in hirsutism, FPHL and seborrhea in small subgroups of patients.“
Jing 2008	Systematic review Systematic review of RCTS on the effects of Diane-35 and metformin in treatment of polycystic ovary syndrome	MEDLINE, the Cochrane Central Register of Controlled Trials and the Chinese National Knowledge Infrastructure up to February 2008	Yes	Not assessed	The primary outcome was hirsutism **Conclusions:** ”Diane-35 could be applied to reduce androgen levels and increase SHBG. Whether its effect on improving hirsutism is superior to that of metformin is unclear“
Koulouri 2008	Systematic review Systematic review of commonly used medical treatments for	Cochrane Central Register of Controlled Trials, MEDLINE (1966 to 2006) and	No	Not assessed	**Conclusions:** ”A significant reduction in hirsutism was found for flu-

Table 5. Overview of published reviews and guidelines (*Continued*)

	hirsutism in women supported by RCTs	EMBASE (1983 to 2006)			tamide, spironolactone, cyproterone acetate combined with an oral contraceptive, thiazolidinediones, oral contracep- tive pills (OCPs), finasteride and metformin but not for placebo. Reduction in F-G score in response to treatment was negatively associated with body mass index (BMI)"
Koulouri 2009	Narrative review Clinical review on management of hirsutism supported by literature	No	No	Not assessed	Different treatment options are discussed with OCPs as first line treatment option. The use of anti-androgens, GNRH analogues and cosmetic procedures are also discussed "Topical and systemic treatments or combinations of the two can adequately control hirsutism in most cases"
Legro 2013	Guideline Evidence-based guideline on diagnosis and treatment of PCOS	Although not fully reported a systematic search appears to have been done	Although not fully reported it appears that a critical appraisal has been performed	GRADE	**Conclusions:** "Hormonal contraceptives are the first-line management for menstrual abnormalities and hirsutism/acne in PCOS. Clomiphene is currently the first-line therapy for infertility; metformin is beneficial for metabolic/

Table 5. Overview of published reviews and guidelines (*Continued*)

					glycemic abnormalities and for improving menstrual irregularities, but it has limited or no benefit in treating hirsutism, acne, or infertility. Hormonal contraceptives and metformin are the treatment options in adolescents with PCOS. The role of weight loss in improving PCOS status per se is uncertain, but lifestyle intervention is beneficial in overweight/obese patients for other health benefits. Thiazolidinediones have an unfavourable risk benefit ratio overall, and statins require further study"
Lumachi 2010	Narrative review Clinical review on management of hirsutism supported by literature	No	No	Not assessed	**Conclusions:** "After an ineffective local approach by direct hair removal, a pharmacological treatment should be suggested, using estrogen and progestin combinations, antiandrogens (i.e. cyproterone acetate, spironolactone) or both as a first line. Finasteride, gonadotropin-releasing hormone agonists, and glucocorticoids should be used in

Table 5. Overview of published reviews and guidelines (*Continued*)

					selected cases. Adequate contraception is also recommended if antiandrogens are used. Unfortunately, since systemic therapy reduces hair growth in less than 50% of cases, hirsute women frequently require cosmetic measures. The use of a logical combination of different options has been shown to achieve a satisfactory result in most cases.“
Martin 2008	Guideline Guideline on evaluation and treatment of hirsutism in premenopausal women	Although not fully reported it appears that a systematic search has been performed	Although not fully reported it appears that a critical appraisal has been performed	GRADE	**Conclusions:** ”For women with patient-important hirsutism despite cosmetic measures, we suggest either pharmacological therapy or direct hair removal methods. For pharmacological therapy, we suggest oral contraceptives for the majority of women, adding an antiandrogen after 6 months if the response is suboptimal. We recommend against antiandrogen monotherapy unless adequate contraception is used. We suggest against using insulin-lowering drugs.“

Table 5. Overview of published reviews and guidelines (*Continued*)

Paparodis 2011	Narrative review Clinical review on diagnosis and management of hirsutism supported by literature	No	No	Not assessed	**Conclusions:** "...therapies proven to be effective are OCPs alone , or in combination with spironolactone, for women not desiring pregnancy. For women with PCOS considering pregnancy, metformin is the treatment of choice. "
Pasquali 2013	Narrative review Clinical review on diagnosis and management of hirsutism in PCOS supported by literature	No	No	Not assessed	**Conclusions:** "Cosmetic procedures and pharmacological intervention are commonly used in the treatment of hirsutism and are discussed in this paper. Importantly, there are different phenotypes of women with hirsutism and PCOS that may require specific attention in the choice of treatment. In particular, when obesity is present,lifestyle intervention should be always considered, and if necessary combined with pharmacotherapy."
Rosenfield 2005	Narrative review Clinical review on diagnosis and management of hirsutism supported by literature	No	No	Not assessed	**Conclusions:** "A trial of eflornithine chloride cream might be tried initially for facial hirsutism,.... I would also encourage weight control. .... If hirsutism re-

Table 5. Overview of published reviews and guidelines (*Continued*)

					mained inadequately controlled. .... I would recommend oral contraceptives, which would be expected to substantially reduce the need for cosmetic treatments over a 9-to-12-month period. I would also discuss the potential permanent benefit, risks, and costs of laser hair removal or electrolysis. For more severe hirsutism, spironolactone could be added to oral-contraceptive therapy, which would require closer monitoring for side effects than would the other options."
Swiglo 2008	Systematic review Systematic review on antiandrogens for the treatment of hirsutism	MEDLINE, EMBASE, and Cochrane CENTRAL (up to May 2006), review of reference lists, and contact with hirsutism experts to identify eligible RCTs	Yes, allocation concealment, blinding of investigators, participants and outcome assessors, attrition bias	GRADE	**Conclusions as stated in text:** "Weak evidence suggests antiandrogens are mildly effective agents for the treatment of hirsutism."

PCOS: polycystic ovary syndrome
RCT: randomised controlled trial

Table 6. Research recommendations based on a gap in the evidence of the effects of interventions for hirsutism excluding laser and photoepilation therapy

Core elements	Issues to consider	Status of research for this review and recommendations
Evidence (E)	What is the current evidence?	This systematic review identified 157 RCTs, of which 109 provided usable data. Ferriman-Gallwey score and serum androgen levels were addressed in most of the studies, adverse events in nearly half of the studies, participant-assessed improvement and change in health-related quality of life in a minority of studies and change in BMI and improvement of other clinical signs of hyperandrogenism were evaluated in around one-third of the studies OCPs, especially with antiandrogenic activity, flutamide and spironolactone are effective for the treatment of hirsutism. There were no consistent results for finasteride. Metformin and lifestyle modification are not effective for hirsutism
Population (P)	Diagnosis, disease stage, comorbidity, risk factors, gender, age, ethnic group, specific inclusion or exclusion criteria, clinical setting	**Inclusion criteria** • Hirsute women with PCOS or idiopathic hirsutism • Ferriman-Gallwey score > 8 **Exclusion criteria** • Thyroid disease, hyperprolactinaemia, and diabetes mellitus • < 3 months before the study, use of any form of oral contraceptives, other steroid hormones, or any other treatments likely to affect ovarian function, insulin sensitivity, or lipid profile • Pregnancy • Androgen-secreting adrenal or ovarian neoplasm • Cushing's syndrome, or congenital adrenal hyperplasia • Intake of medication known or suspected to affect reproductive or metabolic function < 3 months prior to study entry • History of liver disease and/or alcohol abuse, elevated liver enzymes • Contraindication for OCP • Laser or epilation within 2 months • Chemical depilatories within 2 weeks • Bleaching within 1 week • Plucking within 48 hours or shaving within 24 hours before the study
Intervention (I)	Type, frequency, dose, duration, prognostic factor	The study duration should be at least 6 to 12 months Oral contraceptives + androgens (such as cyproterone acetate, flutamide and spironolactone) or oral contra-

Table 6. Research recommendations based on a gap in the evidence of the effects of interventions for hirsutism excluding laser and photoepilation therapy (*Continued*)

		ceptives + 5α inhibitors
Comparison (C)	Type, frequency, dose, duration, prognostic factor	Oral contraceptives, no treatment or another androgen or 5α inhibitors
Outcome (O)	Which clinical or patient-related outcomes will the researcher need to measure, improve, influence, or accomplish? Which methods of measurement should be used?	1. Participant-reported improvement of hirsutism measured at the end of the study or at other site-dependent and clinically important time points. Assessment involving a recognised or validated rating scale (e.g. visual analogue scale (VAS) and Likert scale) 2. Change in health-related quality of life (HRQOL) assessed using any validated or recognised quality of life instrument at the end of the study 3. Proportion of participants who reported an adverse event throughout the study period. Individual serious adverse events reported separately 4. Clinician's assessment of improvement of hirsutism with a standardised and validated scoring system (e.g. Ferriman-Gallwey score), or assessment of hair diameter, rate of growth, and length of hair at the end of the study 5. Change in serum androgen levels (e.g. total testosterone, free testosterone, dehydroepiandrosterone, androstenedione, dihydrotestosterone) and SHBG at the end of the study. 6. Change in BMI at the end of the study 7. Improvement of other clinical signs of hyperandrogenism (e.g. acne, seborrhoea, female pattern hair loss, ovulatory dysfunction) at the end of the study
Time stamp (T)	Date of literature search or recommendation	11 June 2014
Study type	What is the most appropriate study design to address the proposed question?	Randomised controlled trial

BMI: body mass index
OCP: oral contraceptive pill
RCT: randomised controlled trial
SHBG: sex hormone-binding globulin

APPENDICES

Appendix 1. CENTRAL (*The Cochrane Library*) search strategy

#1 MeSH descriptor: [Hirsutism] explode all trees
#2 hirsut*
#3 frazonism
#4 excess*
#5 terminal
#6 hair*
#7 #4 and #5 and #6
#8 unwanted
#9 hair
#10 growth
#11 #8 and #9 and #10
#12 #1 or #2 or #3 or #7 or #11

Appendix 2. MEDLINE (OVID) search strategy

1. unwanted hair growth.mp.
2. (unwanted and hair and growth).ti,ab.
3. exp Hirsutism/
4. hirsut$.mp.
5. frazonism.mp.
6. or/3-5
7. excess$.ti,ab.
8. terminal.ti,ab.
9. hair$.ti,ab.
10. 7 and 8 and 9
11. 1 or 2
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. clinical trials as topic.sh.
17. randomly.ab.
18. trial.ti.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp animals/ not humans.sh.
21. 19 not 20
22. 6 or 10 or 11
23. 21 and 22

Appendix 3. EMBASE (OVID) search strategy

1. exp hirsutism/
2. hirsut$.mp.
3. frazonism.mp.
4. hair$.ti,ab.
5. excess$.ti,ab.
6. terminal.ti,ab.
7. 4 and 5 and 6
8. unwanted.ti,ab.
9. hair.ti,ab.
10. growth.ti,ab.
11. 8 and 9 and 10
12. unwanted hair growth.mp.
13. 1 or 2 or 3 or 7 or 11 or 12
14. crossover procedure.sh.
15. double-blind procedure.sh.
16. single-blind procedure.sh.
17. (crossover$ or cross over$).tw.
18. placebo$.tw.
19. (doubl$ adj blind$).tw.
20. allocat$.tw.
21. trial.ti.
22. randomized controlled trial.sh.
23. random$.tw.
24. or/14-23
25. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
26. human/ or normal human/
27. 25 and 26
28. 25 not 27
29. 24 not 28
30. 13 and 29
31. remove duplicates from 30

CONTRIBUTIONS OF AUTHORS

EvZ was the contact person with the editorial base.

EvZ co-ordinated the contributions from the co-authors and together with ZF wrote the final draft of the protocol.

EvZ and ZF screened papers against the eligibility criteria.

EvZ obtained data on ongoing and unpublished studies.

EvZ and ZF extracted data for the review and sought additional information about papers. BC and NP checked the calculations of EvZ regarding mean changes from baseline for different outcomes.

EvZ entered data into RevMan.

EvZ and ZF analysed and interpreted data. BC and NP assisted where data were pooled.

EvZ, ZF, and BC worked on the methods sections.

EvZ and ZF drafted the clinical sections of the background and responded to the clinical comments of the referees.

EvZ, ZF, BC, and NP responded to the methodology and statistics comments of the referees.

EvZ was the consumer co-author and checked the protocol for readability and clarity. She also ensured that the outcomes are relevant to consumers.

EvZ is the guarantor of the final review.

Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health, UK.

DECLARATIONS OF INTEREST

There are no financial conflicts of interest; the authors, Esther van Zuuren, Zbys Fedorowicz, Ben Carter and Nik Pandis declare that they do not have any associations with any parties who may have vested interests in the results of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support, Netherlands.
- No sources of support, Bahrain.
- No sources of support, UK.

External sources

- No sources of support, Netherlands.
- No sources of support, Bahrain.
- The National Institute for Health Research (NIHR), UK.

The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We judged several of the studies included in this review to be at a substantial risk of bias, which was largely attributable to the significant lack of data on the losses at follow-up. Whilst we made every attempt to ensure accurate and complete data extraction, we used the following algorithm to determine the appropriate judgement for risk of bias due to incomplete data:

- When the overall loss to follow-up (LTFU) was less than 10%, we judged this domain as at 'low' risk of bias.
- When the overall LTFU was between 10% and 20%, and balanced between the arms, we judged this as at 'unclear' risk of bias, and if unbalanced as at 'high' risk of bias.
- When either the overall or each individual arm LTFU was between 20% and 40%, and balanced between the arms, we judged this as at 'high' risk of bias.
- When either the overall or each individual arm LTFU was between 20% and 40%, and not balanced between the arms, or when the overall LTFU was greater than 40% we did not extract the data.

We had planned to compare and present the pooled data for the androgen levels for each comparison. Although we carried out several pooled analyses these have not been presented, based on a decision following discussions with the Editorial board of the Skin Group. The changes in androgen levels have been reported for each individual study in the additional tables.

We had planned to include Web of Science in our searches. However, we considered that the comprehensive search strategy provided sufficient coverage to identify all potentially eligible studies without the additional necessity to search this database.

INDEX TERMS

Medical Subject Headings (MeSH)

5-alpha Reductase Inhibitors [*therapeutic use]; Androgen Antagonists [*therapeutic use]; Body Mass Index; Contraceptive Agents, Female [*therapeutic use]; Cyproterone Acetate [therapeutic use]; Desogestrel [therapeutic use]; Drug Combinations; Eflornithine [therapeutic use]; Ethinyl Estradiol [therapeutic use]; Finasteride [therapeutic use]; Flutamide [therapeutic use]; Hirsutism [*drug therapy]; Hypoglycemic Agents [*therapeutic use]; Metformin [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Spironolactone [therapeutic use]

MeSH check words

Adult; Female; Humans